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EDITED BY N. RASHEVSKY
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The next issue of THE BULLETIN OF MATHEMATICAL BIOPHYSICS (*June, 1939*) will contain the following papers:

ELONGATION AND CONSTRUCTION IN CELL DIVISION, *by* GALE YOUNG.

ON THE SO-CALLED PLASTICITY OF THE CENTRAL NERVOUS SYSTEM, *by* N. RASHEVSKY.

CONTRIBUTIONS TO THE MATHEMATICAL BIOPHYSICS OF THE CENTRAL NERVOUS SYSTEM, *by* H. D. LANDAHL.

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MATHEMATICAL BIOPHYSICS OF CELL RESPIRATION II

H. D. LANDAHL
The University of Chicago

The recent approximate method developed by N. Rashevsky in his book *Mathematical Biophysics* is shown to lead to results equivalent to those obtained in the preceding paper on cell respiration. An estimate is made of the value of the total diffusion resistance to lactic acid for unfertilized *Arbacia* eggs. Several more general reactions are treated to illustrate the effect of intermediate products. Expressions for the glycolytic coefficient are derived in terms of the parameters of the cell.

I

In continuing the theoretical study of cells with particular reference to respiration, we shall first show that the method recently outlined by N. Rashevsky (Rashevsky, 1938) gives results equivalent to those obtained by the previous method. Using the simpler method, we shall then study somewhat more complex interactions.

We first present a brief outline of some results from the Appendix of *Mathematical Biophysics* (Rashevsky, 1938), using slightly different notation. Consider an axially symmetric cell of length approximately $2\,r_1$ and of diameter approximately $2\,r_2$. Let h_i and D_i be the permeability and diffusion coefficients of the substance i. Similarly for the substance i, let c_{0i} be the external concentration, c_{ai} the internal concentration at the ends, c_{bi} the internal concentration at the circumference, and $\bar{c}_i$ the average internal concentration. We have, then, for the net outflow over the ends (Rashevsky, 1938, p. 317)

$$\frac{2\,\pi\,r^2_2}{r_1}\,D_i\,(\bar{c}_i - c_{ai}) = 2\,\pi\,r^2_2\,(c_{ai} - c_{01})\,h_i \tag{1}$$

and for the net radial outflow

$$4\,\pi\,r_1\,D_i\,(\bar{c}_i - c_{bi}) = 4\,\pi\,r_1\,r_2\,(c_{bi} - c_{0i})\,h_i\,, \tag{2}$$

where we have taken $2\,\pi\,r^2_2$ and $4\,\pi\,r_1\,r_2$ as the respective areas.

If q_i is the average rate of *consumption* of substance i and $V = \frac{4}{3}\pi\,r_1\,r^2_2$ is the approximate volume, the total outflow is $-q_i\,V$. Eliminating c_{ai} and c_{bi} from equations (1) and (2), then adding the outflow from (1) and (2) and equating to $-q_i V$, we have, after rearranging,

$$\bar{c}_i = c_{0i} - \Lambda_i q_i \tag{3}$$

where

$$\Lambda_i = \frac{2}{3 h_i D_i} \frac{(r_1 h_i + D_i)(r_2 h_i + D_i) r_1 r_2}{2 r_1 (r_1 h_i + D_i) + r_2 (r_2 h_i + D_i)} . \tag{4}$$

In the case of a sphere, $r_1 = r_2 = r_0$, and we have

$$\Lambda_{is} = \frac{2}{9} \left(\frac{r_0}{h_i} + \frac{r^2{}_0}{D_i} \right) . \tag{5}$$

In section I of the preceding paper (Landahl, 1937), it was assumed that the glucose broke down to lactic acid at a rate proportional to its own concentration; that the lactic acid was resynthesized at a rate proportional to the square of its concentration; and that the lactic acid was oxidized at a rate proportional to the product of its concentration with that of oxygen. Instead of the differential equations previously obtained, we have, upon using Rashevsky's recent method, the algebraic equations

$$q_1 = a \bar{c}_1 - b \bar{c}^2{}_2 , \tag{6}$$

$$q_2 = n f \bar{c}_2 \bar{c}_3 + b \bar{c}^2{}_2 - a \bar{c}_1 , \tag{7}$$

$$q_3 = f \bar{c}_2 \bar{c}_3 . \tag{8}$$

Substituting equation (3) into the above equations, we obtain

$$q_1 = a (c_{01} - \Lambda_1 q_1) - b (c_{02} - \Lambda_2 q_2)^2 , \tag{9}$$

$$q_2 = n q_3 - q_1 , \tag{10}$$

$$q_3 = f (c_{02} - \Lambda_2 q_2)(c_{03} - \Lambda_3 q_3) . \tag{11}$$

Equations (9), (10) and (11) may be written

$$A q^2{}_2 - B q_2 + C q_1 - D = 0 , \tag{12}$$

$$q_1 + q_2 - n q_3 = 0 , \tag{13}$$

$$H q_2 q_3 - K q_3 - M q_2 + S = 0 , \tag{14}$$

where

$$\begin{aligned} A &= b \Lambda^2{}_2 , & H &= f \Lambda_2 \Lambda_3 , \\ B &= 2 b c_{02} \Lambda_2 , & K &= 1 + f c_{02} \Lambda_3 , \\ C &= a \Lambda_1 + 1 , & M &= f c_{03} \Lambda_2 , \\ D &= a c_{01} - b c^2{}_{02} , & S &= f c_{02} c_{03} . \end{aligned} \tag{15}$$

Equations (12), (13) and (14) are the same as equations (22), (23) and (24) of the preceding paper (Landahl, 1937) so that the subsequent relations are formally alike. Equations (15) are the same as equations (25) of the previous paper if ε_1 and ε_2 are neglected, and if we use the above equation (4) for the definition of Λ_i. In the case for which $b = 0$, the solution of equations (12), (13) and (14) for q_3 is given by equation (66) of the previous paper, in the form $(c_{03} \equiv x)$

$$c_{03} = \beta\, y + \frac{\alpha\, y}{1 - y} \tag{16}$$

where $y = q_3/q_{3l}$, and q_{3l} is the limiting value of q_3, and

$$\alpha = \frac{1}{n\, f\, \Lambda_2}, \qquad n = \frac{180}{192} = .94 \tag{17}$$

$$\beta = \Lambda_3\, q_{3l} = \frac{\Lambda_3}{n\, \Lambda_2\, (a\, \Lambda_1 + 1)} \left[(a\, \Lambda_1 + 1)\, c_{02} + a\, c_{01}\, \Lambda_2 \right] . \tag{18}$$

In equation (4) let us substitute

$$r_1 = \xi\, r_2\, , \qquad \xi \geq 1\, . \tag{19}$$

ξ is taken as greater than or equal to one since this is the more general occurrence. The results which follow will hold also for $\xi < 1$, but if not too small a fraction, i.e., for not too flat cells. We then obtain, omitting the index i,

$$\Lambda = \frac{2}{3\,D\,h}\, \frac{(\xi\, r_2\, h + D)\, (r_2\, h + D)\, \xi\, r_2}{2\, \xi\, (\xi\, r_2\, h + D) + (r_2\, h + D)} \, . \tag{20}$$

Differentiating Λ with respect to ξ, we obtain

$$\frac{d\,\Lambda}{d\,\xi} = \frac{2}{3} \left[\frac{r_2}{h} + \frac{r^2_2}{D} \right] \frac{(2\, \xi\, r_2\, h + D)\, (r_2\, h + D)}{[2\, \xi\, (\xi\, r_2\, h + D) + (r_2\, h + D)]^2} > 0\, . \tag{21}$$

Now for $\xi = 1$, we have $\Lambda = \Lambda_s$ of equation (5). For $\xi \doteq \infty$, or $r_1 >> r_2$, we have

$$\Lambda_{(r_1 >> r_2)} \doteq \frac{1}{3} \left[\frac{r_2}{h} + \frac{r^2_2}{D} \right] = \frac{3}{2}\, \Lambda_s \tag{22}$$

where for r_0 we use r_2 the cylindrical radius. Since Λ increases with ξ from Λ_s to $\frac{3}{2}\Lambda_s$ so that the order of magnitude of Λ does not change with ξ, we may use the simpler expression Λ_{is} of equation (5) instead of Λ_i of equation (4). Comparing the value of Λ (Λ_s) of equation (5) with the definition of Λ in equation (25) of the previous method (Landahl, 1937) we see that inequalities corresponding to the previously derived equations (71) and (72) would lead to slightly larger values for h and values of D which are about three times as large.

The value of Λ is determined both by the permeability, h, and the internal diffusion coefficient, D. The values of h and D are not determined even approximately, without additional information. For this reason it is often convenient to use Λ without reference to the permeability and diffusion coefficients. Λ_i measures the resistance to the flow of the substance i due to both the internal diffusion and the diffusion through the membrane. We may then refer to Λ as the *total diffusion resistance*. Λ has the dimension of time. The larger the Λ, the longer is the time required for a given amount of substance to enter or leave the cell in a nonstationary diffusion state.

II

Let us now make an estimate of the value of the total diffusion resistance Λ_2 for lactic acid and the coefficient f [equation (8)] on the basis of data available for unfertilized *Arbacia* eggs. For low values of the external oxygen concentration c_{03}, the rate of oxygen consumption, q_3, is limited by the value of c_{03} and is proportional to it, while the value of the concentration of lactic acid $\bar{c}_2$ is relatively constant. For large values of c_{03}, the concentration of oxygen in the cell, $\bar{c}_3$, is high and stable, but the oxygen consumption is limited by the rate of production of lactic acid. (The latter holds if the glycolytic coefficient is very low; it is probably low enough in the case of unfertilized *Arbacia* eggs. See later discussion.) Then near the point of maximum curvature of the $y(x)$ curve, $x \equiv c_{03}$, both factors are of the same order of importance. If, at this point, $\bar{c}_2 = c^*_2$, $\bar{c}_3 = c^*_3$, and $q_3 = q^*_3$ approximately, then, as in equation (8), we may write

$$q^*_3 = f\, c^*_2\, c^*_3 . \tag{23}$$

From the preceding discussion it follows that c^*_2 and c^*_3 are of the order of but less than the maximum values. Hence very roughly we may put $c^*_2 = \frac{1}{2}\, \bar{c}_{2\,\max}$ and $c^*_3 = \frac{1}{2}\, c^*_{03}$. From equation (17)

$$\Lambda_2 = \frac{1}{\alpha\, n\, f} \doteq \frac{c^*_2\, c^*_3}{\alpha\, q^*_3} . \tag{24}$$

Taking $\bar{c}_{2\,\max} = 2 \times 10^{-4}$. gm./cc. as the approximate concentration of lactic acid in the unfertilized *Arbacia* eggs (Perlzweig and Barron, 1928); and $\alpha = 12 \times 10^{-8}$ gm./cc., $c^*_{03} = 6 \times 10^{-7}$ gm./cc. and $q^*_3 = .35 \times 10^{-5}$ gm./cc./min. $= 6 \times 10^{-8}$ gm./cc./sec. as the approximate values obtained previously (Landahl, 1937) from the data by Tang (1931), we have

$$\begin{aligned} f &\backsim 10^5 \text{ cc./gm./min.} = 2 \times 10^3 \text{ cc./gm./sec.} \\ \Lambda_2 &\backsim .8 \times 10^2 \text{ min.} = 5 \times 10^3 \text{ sec.} \end{aligned} \tag{25}$$

In order that Λ_2 have the value estimated, we have, using the inequalities of equations (71) and (72) (Landahl, 1937)

$$\begin{aligned} D_2 &> 10^{-8} \text{ cm.}^2\text{/min.} = 2 \times 10^{-10} \text{ cm.}^2\text{/sec.} \\ h_2 &\backsim 2 \times 10^{-5} \text{ cm./min.} = 3 \times 10^{-7} \text{ cm./sec.} \end{aligned} \tag{26}$$

The concentration of lactic acid in the fertilized eggs is but slightly more than that in unfertilized eggs (Perlzweig and Barron, 1928). The oxygen consumption q_{3l} is, however, four or five times as great. Since the other values are not very different, Λ_2 for fertilized *Arbacia* eggs is several times smaller than that for unfertilized eggs.

Comparing the above values with that previously obtained for D_3 and h_3, we see that they differ by a factor of 10^3. On the basis of physical considerations one would not expect the diffusion coefficients for lactic acid and oxygen to differ by such an order of magnitude even though the former should drag larger molecules with it. On the basis of Stoke's Law and the previous limit estimated,

$$D_3 \underset{\backsim}{>} 10^{-5} \text{ cm.}^2\text{/min., a value } D_2 \underset{\backsim}{>} 10^{-5}, 10^{-6} \text{ cm.}^2\text{/min.,}$$

would seem plausible. Hence the symbols are as chosen above in (26). The rough estimate gives a value for the permeability of lactic acid (lactate) of the same order of magnitude as that for glycerol obtained by other methods (Jacobs and Stewart, '32).

Equation (18), rewritten as

$$q_{3l} = \frac{1}{n} \left[\frac{c_{02}}{\Lambda_2} + \frac{a\, c_{01}}{a\, \Lambda_1 + 1} \right], \tag{27}$$

gives the $q_{3l}(c_{02})$ relation and $n\, \Lambda_2$ is the reciprocal of the initial slope. It would be of interest to compare the more direct evaluation of Λ_2 from the experimental relation $q_{3l}(c_{02})$ with the estimate made above. In the event that the experimental procedure to determine this relation is straightforward, it would furnish a method for the study of various factors on the membrane's permeability to lactic acid. Among the factors of particular interest would be fertilization. However, for cases of large glycolysis certain difficulties arise, to be discussed later [equation (84), seq.].

III

Let us now consider a somewhat more general case in which the resynthesis occurs by two routes, one direct and proportional to $b\,\bar{c}^2_2$ and the other coupled to the energy from the oxidation of lactic acid so that this part of the resynthesis is proportional to the oxygen consumed, $\nu\, f\, \bar{c}_2\, \bar{c}_3$. Instead of equations (6), (7) and (8) we have

$$q_1 = a\,\bar{c}_1 - b\,\bar{c}^2_2 - \nu\, f\,\bar{c}_2\,\bar{c}_3\,, \tag{28}$$

$$q_2 = n\, f\,\bar{c}_2\,\bar{c}_3 - a\,\bar{c}_1 + b\,\bar{c}^2_2 + \nu\, f\,\bar{c}_2\,\bar{c}_3\,, \tag{29}$$

$$q_3 = f\,\bar{c}_2\,\bar{c}_3\,. \tag{30}$$

Substituting equation (3) into the above set of equations and rearranging, we have, using equations (15),

$$\nu\, H\, q_2\, q_3 + A\, q^2_2 - (B + \nu\, M)\, q_2 - \nu (K - 1)\, q_3 + C\, q_1 - D + \nu\, S = 0\,, \tag{31}$$

$$q_1 + q_2 - n\, q_3 = 0\,, \tag{32}$$

$$H\, q_2\, q_3 - K\, q_3 - M\, q_2 + S = 0\,. \tag{33}$$

Multiplying equation (33) through by ν and subtracting from (31), the latter may be written

$$A\, q^2_2 - B\, q_2 + C\, q_1 - D + \nu\, q_3 = 0\,, \tag{34}$$

Substituting for q_1 from equation (32) into (34) we obtain

$$A\, q^2_2 - (B + C)\, q_2 + (n\, C + \nu)\, q_3 - D = 0\,. \tag{35}$$

Comparing equation (35) with the equation resulting from the elimination of q_1 from equations (12) and (13) of the preceding case, it is evident that n is replaced by $(n + \frac{\nu}{C})$. Since $(n\, C + \nu)$ is constant and independent of c_{03} and since equations (14) and (33) are identical, the form of the $q_3(c_{03})$ relation, in particular, is unchanged. If the resynthesis is considered only coupled with oxidation so that b is taken equal to zero, we have as in equation (16)

$$c_{03} = \beta\, y + \frac{\alpha\, y}{1 - y} \tag{36}$$

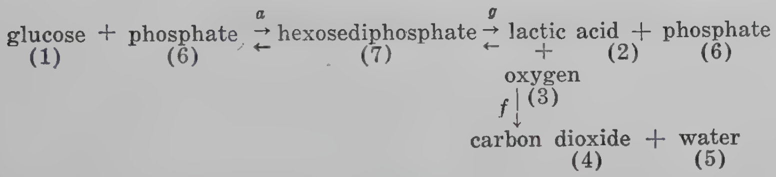
where now

$$\alpha = \frac{(a\,\Lambda_1 + 1)}{f\,\Lambda_2[n(a\,\Lambda_1 + 1) + \nu]} \tag{37}$$

$$\beta = \Lambda_3\, q_{3l} = \frac{\Lambda_3}{\Lambda_2}\,\frac{[(a\,\Lambda_1 + 1)\, c_{02} + a\, c_{01}\,\Lambda_2]}{[n(a\,\Lambda_1 + 1) + \nu]}\,. \tag{38}$$

IV

The mechanisms of respiration thus far discussed are extremely simplified when one considers the actual processes which probably occur.* Let us now consider the effect of an intermediate product which does not leave the cell and which contains a radical which in no form leaves the cell. Consider the following reaction (Cameron, 1930):



Let us assume that the phosphate in no form leaves the cell, so that the total amount of phosphate per unit volume is a constant c_P. For simplicity we shall not consider the reactions as reversible. Also, the equations for carbon dioxide and water shall be omitted. Then if the subscript 6 refers to the phosphate and 7 to the hexosediphosphate, and if $m = 2\,M_6/M_7$ and again $n = 2\,M_2/6\,M_3$, where M_i is the molecular weight of substance i, we have the following equations:

$$q_1 = a\,\bar{c}_1\,\bar{c}_6\,, \tag{39}$$

$$q_2 = n\,f\,\bar{c}_2\,\bar{c}_3 - g\,\bar{c}_7\,, \tag{40}$$

$$q_3 = f\,\bar{c}_2\,\bar{c}_3\,, \tag{41}$$

$$q_6 = -q_7 = a\,\bar{c}_1\,\bar{c}_6 - g\,\bar{c}_7 = 0\,, \tag{42}$$

$$c_P = \bar{c}_6 + m\,\bar{c}_7\,. \tag{43}$$

Consider, first, the anaerobic case so that $\bar{c}_3 = q_3 = 0$. Then solving for $\bar{c}_7$ in equation (43) and substituting into (42) and rearranging, we have

$$\bar{c}_6 = \frac{g\,c_P}{a\,m\,\bar{c}_1 + g}\,. \tag{44}$$

Substituting for $\bar{c}_6$ the above value and using the relation $\bar{c}_1 = c_{01} - \Lambda_1\,q_1$, we have, on clearing,

$$a\,m\,\Lambda_1\,q_1^2 - [\,a\,m\,c_{01} + a\,g\,c_P\,\Lambda_1 + g]\,q_1 + a\,g\,c_{01}\,c_P = 0\,. \tag{45}$$

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* For summary and bibliography see Burk (1937).

For sufficiently small values of c_{01}, and hence q_1,

$$q_1 = \frac{a\,c_P}{a\,c_P\,\Lambda_1 + 1}\,c_{01} \tag{46}$$

and for sufficiently large values of c_{01}, q_1 approaches the limit

$$q_{1l} = \frac{g\,c_P}{m}\,. \tag{47}$$

If $z = q_1/q_{1l}$, then equation (45) may be written

$$c_{01} = \zeta\,z + \frac{\eta\,z}{1 - z} \tag{48}$$

where

$$\eta = \frac{g}{a\,m} \tag{49}$$

$$\zeta = \frac{g\,c_P\,\Lambda_1}{m} = \Lambda_1\,q_{1l}\,\cdot \tag{50}$$

Equation (48) is of the same form as equation (16) and may be illustrated by the curve in Figure 1, which is drawn to approximate the experimental values for fructose obtained graphically from data

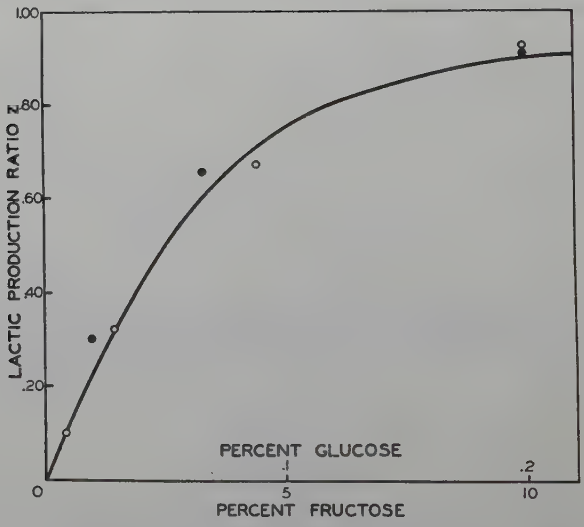

FIGURE 1

The lactic acid production ratio, $z = q_1/q_{1l}$, is plotted against the concentration of fructose [°] (Boyland and Boyland, '38) and glucose [.] (Warburg, '26). For fructose, the value of q_{1l} was taken as 6.9×10^{-6} gm./cc./sec. and for glucose 8.8×10^{-6} gm./cc./sec. Note that the abscissa scale is different for each.

by Boyland and Boyland, (1938). The experimental points for glucose are by Warburg et al. (Warburg, 1926, p. 121). Since the values of the lactic acid production are not given for higher sugar concentrations, the highest value in each case was taken about ninety per cent of a theoretical maximum. The origin for the ordinates was taken, in both cases, as the value of the lactic acid production for zero concentration of hexose in the experiments by Boyland and Boyland. Since the number of experimental points in each case is so few and since the origin for the curve in one case is not certain, and the limits in neither case can be estimated with any accuracy, no attempt is made to evaluate any of the parameters.

Because there are so few points, it is not possible, to say that the curves for glucose and fructose are significantly the same or different. But if the curves did coincide in the figure, then $\eta_{fr} = 20\ \eta_{gl}$ and $\zeta_{fr} = 20\,\zeta_{gl}$, where the subscripts refer to fructose and glucose, and the factor twenty arises because there happens to be a factor of twenty between the two scales. Since the limiting values of the lactic acid product is nearly the same in each (Boyland and Boyland, 1938), then by equation (50) we have $\Lambda_{1fr} = 20\ \Lambda_{1gl}$ or the total diffusion resistance for fructose is twenty times that for glucose. If we assume also that the secondary stage is to a large extent the same in both cases, so that c_P is nearly the same in each, then, since m is the same for both, g must be the same for both to satisfy equation (50). In other words the second stage reaction goes at about the same rate in both. In this case one might then tentatively assume the secondary reactions to be largely equivalent. From equation (49) we have $a_{gl} = 20\ a_{fr}$, so that the rate of formation of the second product, hexosediphosphate, from glucose is twenty times the rate of its formation from fructose. However, it could very well be that, at least in some instances, the two curves could not possibly be made to coincide by a linear change in the abscissa scale. In this case it would not be possible to compare the total diffusion resistance or other constants directly; but it would be necessary to fit the curves empirically to evaluate η and ζ. Λ_1 would then be given, but in general, an additional empirical relation would be required to evaluate a, g, and c_P.

In experiments on tissue extracts (Haarmann and Stratmann, 1932) the results indicate an initial increase of glycolysis with sugar concentration and, in most cases, a decrease at higher values. The values are, however, quite erratic. In experiments on yeast fermentation (Hopkins and Roberts, 1935) excellent curves are obtained. The initial rise is of the form of equation (48), but for rather high values of sugar concentration the fermentation rate drops very slowly. (The ratio of the initial slope to the final slope is approximately minus fifty for glucose and minus one hundred for fructose.) The conditions in the two above cases are not directly applicable but are mentioned because of their similarity to the case under discussion.

If the supply of glucose is more than a few tenths per cent, $q_1 \doteq q_{1l}$. The aerobic case is then simplified and the result becomes a special case of section II of the preceding paper (Landahl, 1937). By analogy, we may write

$$c_{03} = \beta y + \frac{\alpha y}{1 - y} \tag{51}$$

where

$$\alpha = \frac{1}{n f \Lambda_2} \tag{52}$$

$$\beta = \Lambda_3 q_{3l} = \frac{\Lambda_3}{n \Lambda_2} \left(c_{02} + \frac{g c_P}{m} \Lambda_2\right). \tag{53}$$

V

The glycolytic coefficient (Rashevsky, 1938, p. 105) β' or Glykolyse/Atmung (Warburg, 1926, p. 126) is defined by the ratio of the number of lactic acid molecules produced by glycolysis which are not oxidized to the number of oxygen molecules consumed. Or we may say that $3\beta'$ is the ratio of the number of molecules of lactic acid glycolyzed to the number oxidized. The symbol β' is the same as the β used by Rashevsky (1938) and is not to be confused with the β used here. Then

$$\beta' = \frac{-q_2}{M_2} \frac{M_3}{q_3} = \frac{-q_2}{3 n q_3} \; ; n = \frac{M_2}{3 M_3}. \tag{54}$$

Solving for q_2 in equation (14), (33) or (41) and substituting above,

$$\beta' = \frac{q_3 - f c_{02} (c_{03} - \Lambda_3 q_3)}{3 n f \Lambda_2 q_3 (c_{03} - \Lambda_3 q_3)}. \tag{55}$$

Since $y = q_3/q_{3l}$ and $\beta = \Lambda_3 q_{3l}$, we have, using equation (16), (36) or (51),

$$c_{03} - \Lambda_3 q_3 = c_{03} - \beta y = \frac{\alpha y}{1 - y}. \tag{56}$$

We may then write for equation (55), using equations (37) and (38) quite arbitrarily,

$$\beta' = \frac{n(a \Lambda_1 + 1) + \nu}{3n[(a \Lambda_1 + 1) c_{02} + a c_{01} \Lambda_2]} \left[\frac{a c_{01} \Lambda_2}{(a \Lambda_1 + 1)} \frac{(1 - y)}{y} - c_{02}\right], \tag{57}$$

from which it is evident that β' decreases with c_{02}, the external lactate concentration. In a great deal of experimental work (Warburg, 1926) the value of c_{02} is negligible and for this condition

$$\beta' = \frac{1}{3}\left[1 + \frac{\nu}{n(a\,\Lambda_1 + 1)}\right]\frac{1-y}{y}. \tag{58}$$

For small values of the external oxygen concentration, c_{03}, and hence small y, equation (58) may be written

$$\beta' = \frac{1}{3\,n}\left[\frac{1}{f\,\Lambda_2} + \frac{a\,c_{01}\,\Lambda_3}{(a\,\Lambda_1 + 1)}\right]\frac{1}{c_{03}} \tag{59}$$

and for values of y not too far from unity.

$$\beta' = \frac{1}{3\,n\,f\,\Lambda_2\,c_{03}}. \tag{60}$$

For sufficiently large values of the external oxygen concentration c_{03}, β' approaches zero (or becomes negative if $c_{02} \neq 0$). The coefficient β' is inversely proportional to c_{03}. For a constant, not too high value of c_{03}, β' increases with decreasing total diffusion resistance Λ_2; and to a lesser extent β' increases as the external glucose concentration, c_{01}, increases; as the total diffusion resistance to oxygen, Λ_3, increases, and as the total diffusion resistance to glucose, Λ_1, decreases. Also β' decreases with f and to a lesser extent increases with a. These results for the variation of β' are essentially dependent only on the assumptions involved in obtaining equation (8), and hence apply to all the preceding cases. However, in the following case the expression for the glycolytic coefficient, though similar in some respects, will differ in the respect that for large oxygen concentrations β' may remain large and positive.

VI

Let us now consider a still more complex system and discuss some of its properties. Consider a system in which a sugar is glycolized through the hexosediphosphate stage into lactic acid. The mechanism through which lactic acid is oxidized is complex. That in some instances intermediate stages are pyruvic acid, acetaldehyde, acetic acid and alcohol has been suggested (Cameron, 1930). Let us assume that the intermediate products do not appreciably leave the cell and consider a net reaction in which lactic acid must be in contact with a catalytic substance K, i.e., form a "complex," in order that oxidation may occur.* We then have the following system:

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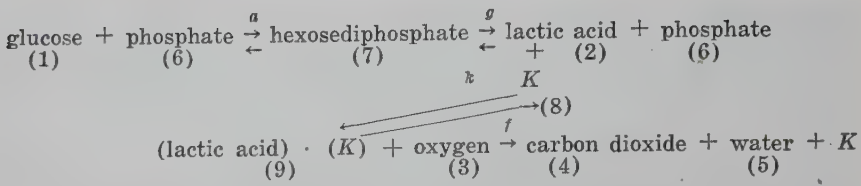
* It is also assumed that the catalytic substance does not leave the cell. However, certain enzymes leave the cells in sufficient quantity so that the filtrate may be studied with respect to its metabolism (Rubenstein, 1933).


glucose + phosphate $\overset{a}{\rightleftarrows}$ hexosediphosphate $\overset{g}{\rightleftarrows}$ lactic acid + phosphate
(1) (6) (7) + (2) (6)
k K
(8)
f
(lactic acid) · (K) + oxygen → carbon dioxide + water + K
(9) (3) (4) (5)

The number under each substance is the subscript number, and c_K is the total catalytic substance per unit volume. Considering only the forward reactions, we may write the following equations:

$$q_1 = a\,\bar{c}_1\,\bar{c}_6\,, \tag{61}$$

$$q_2 = -g\,\bar{c}_7 + n\,k\,\bar{c}_2\,\bar{c}_8\,, \tag{62}$$

$$q_3 = f\,\bar{c}_3\,\bar{c}_9\,, \tag{63}$$

$$q_6 = -q_7 = a\,\bar{c}_1\,\bar{c}_6 - g\,\bar{c}_7 = 0\,, \tag{64}$$

$$q_8 = -q_9 = k\,\bar{c}_2\,\bar{c}_8 - f\,\bar{c}_3\,\bar{c}_9 = 0\,, \tag{65}$$

$$c_P = \bar{c}_6 + m\,\bar{c}_7\,, \tag{66}$$

$$c_K = \bar{c}_8 + l\,\bar{c}_9\,. \tag{67}$$

As in section IV let us consider that the supply of glucose is ample so that the above set of equations reduces to

$$q_1 = q_{1l}\,, \tag{68}$$

$$q_2 = -q_{1l} + n\,q_3\,, \tag{69}$$

$$q_3 = f\,\bar{c}_3\,\bar{c}_9 = k\,\bar{c}_2\,\bar{c}_8\,, \tag{70}$$

together with equations (67) and (3). Eliminating $\bar{c}_8$, $\bar{c}_9$, q_1 and q_2 from equations (67), (68), (69) and (70) and using equation (3) we obtain after rearranging,

$$\begin{aligned}[n\,k\,l\,\Lambda_2 + f\,\Lambda_3(1 + n\,k\,c_K\,\Lambda_2)]\,q_3^2 - [\,(c_{02} + \Lambda_2\,q_{1l})\\ \times (k\,l + k\,f\,c_K\,\Lambda_3) + (n\,k\,c_K\,\Lambda_2 + 1)f\,c_{03}]\,q_3\\ + k\,f\,c_K(c_{02} + \Lambda_2\,q_{1l})\,c_{03} = 0\,,\end{aligned} \tag{71}$$

which can be given the same form as equation (16). For $c_{03} = \infty$, $q_3 = q_{3l}$, and

$$q_{3l} = \frac{k\,c_K(c_{02} + \Lambda_2\,q_{1l})}{n\,k\,c_K\,\Lambda_2 + 1}\,. \tag{72}$$

Equation (71) may then be written

$$c_{03} = \beta y + \frac{\alpha y}{1 - y} \tag{73}$$

where in this case

$$\alpha = \frac{k\, l (c_{02} + \Lambda_2 q_{1l})}{f (n k c_K \Lambda_2 + 1)^2} \tag{74}$$

$$\beta = \frac{(n k l \Lambda_2 + f \Lambda_3 + n k f c_K \Lambda_2 \Lambda_3)(c_{02} + \Lambda_2 q_{1l}) k c_K}{f (n k c_K \Lambda_2 + 1)^2} . \tag{75}$$

If there is an ample supply of the catalytic substance K present, we may let c_K approach infinity in equation (71) and obtain

$$[n \Lambda_2 \Lambda_3]\, q^2_3 - [\Lambda_3 (c_{02} + \Lambda_2 q_{1l}) + n \Lambda_2 c_{03}]\, q_3 + (c_{02} + \Lambda_2 q_{1l}) c_{03} = 0 \tag{76}$$

which may be written

$$(1 - y)(c_{03} - \beta y) = 0 , \tag{77}$$

with β defined by equation (53). An equation of the form of (76) is obtained if equation (70) is replaced by $q_3 = f \bar{c}_2 \bar{c}_3$ [equation (8)], and if Λ_2 is very large, i,e., α is negligible. The latter restriction arises because of the assumption that the lactic acid catalyst does not leave the cell. In equation (77) the oxygen consumption increases linearly with oxygen concentration until it reaches its limit, after which it is independent of c_{03}. The equation (8) then corresponds to a special case of a reaction requiring a catalyst but in which the catalyst occurs in sufficient quantity not to be a limiting factor.

VII

The expression for the glycolytic coefficient for the case just preceding, in which the sugar supply is large, is given by substituting the value of q_2 given by equation (69) into (54). We then obtain

$$3\beta' = \frac{-q_2}{n q_3} = \frac{q_{1l}}{n q_3} - 1 = \frac{q_{1l}}{n q_{3l} y} - 1 . \tag{78}$$

For small values of the oxygen consumption, β' is evidently large and unstable. Hence let us only investigate the variation of β' for fairly large values of c_{03}, where approximately $c_{03} = \alpha y/(1 - y)$. Then

$$3\beta' = \frac{q_{1l} - n k c_K c_{02}}{n k c_K (c_{02} + q_{1l} \Lambda_2)} + \frac{q_{1l}\, l}{n f c_K (n k c_K \Lambda_2 + 1) c_{03}} , \tag{79}$$

and β' decreases to a certain extent with the external concentrations of oxygen and decreases with the external lactate to a negative limit. Very frequently in experiments *in vitro* the external lactate is negligible and the oxygen tension is sufficiently high so that the consumption of oxygen is independent of the latter. It is under these conditions that the glycolytic coefficient is generally obtained. For this case we have for the glycolytic coefficient

$$\beta' = \frac{1}{3\, n\, k\, c_K\, \Lambda_2} . \tag{80}$$

Now if for some reason certain cells undergo an irreversible change in which the available substance K is decreased, the total diffusion resistance to lactic acid Λ_2 is decreased, or the reaction rate k is decreased, the coefficient β' would increase in inverse proportion.

Now for large c_{03}, we readily find that

$$q_{2(c_{03}\to\infty)} = -\frac{q_{1l} - n\, k\, c_K\, c_{02}}{n\, k\, c_K\, \Lambda_2 + 1} . \tag{81}$$

For normal cells 3 β' is much less than unity, seldom over one-tenth, so that $n\, k\, c_K\, \Lambda_2 >> 1$, and again neglecting c_{02}, we have, with close approximation

$$q_{2(c_{03}\to\infty)} = -3\, \beta'\, q_{1l} , \tag{82}$$

and only a small part of the sugar consumed is produced as lactate. For cancerous cells 3 β' is of the order of one and often several times larger. For the more extreme cases we may write roughly

$$q_{2(c_{03}\to\infty)} \doteq -q_{1l}, \tag{83}$$

that is, nearly all the sugar consumed per unit time, q_{1l}, is transformed into lactic acid which leaves the cell.

For normal cells we have for the limit of the oxygen consumption, from equations (72) and (50),

$$q_{3l} = \frac{1}{n} \left(\frac{c_{02}}{\Lambda_2} + \frac{g\, c_P}{m}\right) . \tag{84}$$

Equation (84) is the counterpart of equation (27) when c_{01} is above the value at which it no longer appreciably affects the sugar consumption. The $q_{3l}(c_{02})$ relation in this case also gives Λ_2 as in equation (27). However, as we pass to cells with larger values of β' the error in Λ_2 obtained from the $q_{3l}(c_{02})$ relation of equation (84) or (27) becomes larger, and for the more extreme cases

$$q_{3l} \doteq k\, c_K (c_{02} + \Lambda_2\, q_{1l}) . \tag{85}$$

The slope of the $q_{3l}(c_{02})$ tends to become independent of Λ_2, and, instead of measuring the reciprocal of Λ_2, it measures the product of the reaction rate k and the total catalytic substance c_K.

Equation (45) or (48) gives the relation between the aerobic production of lactic acid and external concentration of glucose. It would be of decided interest to compare accurately obtained experimental relations for both normal and cancerous cells of similar tissues under identical experimental conditions and over a wide range of values. It might then be possible to determine whether the difference is primarily due to a change in permeability, or to the change of the chemical reaction rates a or g, or, finally to the catalytic action of c_P. Additional knowledge would be obtained by the use of well known inhibitory agents. According to equations (49) and (50) the limit of the rate of glucose consumption, q_{1l}, does not depend on the total diffusion resistance to glucose, Λ_1, or on the reaction rate a, but the shape of the curve does.

Similar parallel studies on the same kind of normal and pathological tissue for the determination of the relation between the aerobic production of lactic acid and the external lactate concentration and the relation between the oxygen consumption and oxygen concentration, $q_3(c_{03})$, should lend some insight into the problem of malignancy. There are in the literature reports of a large number of experiments for some of the relations needed [for $q_3(c_{03})$ relations see summary by Tang (1933)] and less on others. But the material used and the experimental conditions vary so much that any systematic study of the results from the point of view outlined above becomes difficult and of questionable value. It might be emphasized that, though the particular reaction mechanisms considered have some empirical justification, they should be considered as approximations to certain experimental conditions and are given to illustrate certain types of reactions. It is of interest to note that the relation between oxygen consumption and oxygen concentration, $q_3(c_{03})$, is the same in all the cases discussed. [Cf. equations (40), (58) and (66) of the first paper and the above equations (16), (36), (51), (73). The previously obtained equations (40), (58) were not of the same analytic form but could not be distinguished graphically except perhaps under very favorable conditions.] If β in the above mentioned equations is fairly small we may write with very close approximation

$$c_{03} \doteq \frac{\alpha y}{1 - y} \tag{86}$$

or

$$q_3 \doteq \frac{q_{3l}\, c_{03}}{\alpha + c_{03}}. \tag{87}$$

The equation in the form above has been empirically tested by Tang for a large number of cases (Tang, 1933).

Summary

The recent approximate method developed by N. Rashevsky is shown to lead to results equivalent to those obtained in the preceding paper on cell respiration. It is shown that, over a large range, many of the results are not dependent upon the cell shape. The results are simplified by the definition of Λ as the total diffusion resistance, the resistance to flow due to both the diffusion through the cell membrane and through the cell itself. Using information from various sources, an estimate is made of the total diffusion resistance to lactic acid, Λ_2, and the reaction rate constant f for unfertilized *Arbacia* eggs.

Several more general reactions are considered, such as the effect of the resynthesis being coupled to the energy of oxidation; also the effect of an intermediate stage in glycolysis, such as hexosediphosphate; and the effect of a catalytic material required for the oxidation process. Expressions for the glycolytic coefficient are derived in terms of the parameters of the cell. An outline for a series of experiments is given, which, it is suggested, would be of decided value to various problems, especially to the problem of malignancy.

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NOTE ON BIOLOGICAL PERIODICITIES

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The approximation method, recently developed by N. Rashevsky, is applied to a problem of periodic cell reactions, studied exactly in a previous publication. The fundamental features of that previous investigation are thus obtained in a rather simple way.

In a previous publication (Weinberg, 1938)*, we have demonstrated that in an idealized cell in which two coupled monomolecular reactions are proceeding, periodic variations in the concentrations of the reacting substances may be expected, at least if certain relations exist between the reaction constants and the diffusion coefficients of the substances involved. The method used was quite complicated, depending, as it did, upon the solution of a pair of partial differential equations; moreover the results were valid only for the special case in which $\frac{h_1}{D_1} = \frac{h_2}{D_2}$ where h_i and D_i are the permeability and diffusion coefficient, respectively, of the *i*th reacting substance.

Since the appearance of this article, Rashevsky (1938a) has developed an approximate method for handling diffusion problems which simplifies enormously the mathematical detail required for the solution of these problems, and which enables one to treat cases which are much too complicated to be handled rigorously. In this note we shall show how this approximate scheme leads very directly to our previous results, and how it enables us to obtain, approximately, the periods in cases in which $\frac{h_1}{D_1} \neq \frac{h_2}{D_2}$.

Let us again consider a spherical cell of radius r_0, in which two substances whose average concentrations are $\bar{c}_1$ and $\bar{c}_2$ are being produced according to the law

$$\begin{aligned}\text{Rate of production of } \bar{c}_1 &= A_{11}\,\bar{c}_1 + A_{12}\,\bar{c}_2 \\ \text{Rate of production of } \bar{c}_2 &= A_{21}\,\bar{c}_1 + A_{22}\,\bar{c}_2 .\end{aligned} \tag{1}$$

As will be seen presently, the introduction of the average concentrations reduces the partial differential equations previously obtained to ordinary ones.

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* Referred to as (A).

If c_1^* is the concentration of the first substance just inside the cell membrane, it is clear that the average concentration gradient of this substance is $\frac{\bar{c}_1 - c_1^*}{r_0}$. Fick's law then gives for the average amount of material passing through a square centimeter of surface at the cell wall,

$$\frac{D_1(\bar{c}_1 - c_1^*)}{r_0},$$

and since the total area of the cell surface is $4\pi r^2_0$, the total amount passing through the cell wall is $4\pi r_0 D_1(\bar{c}_1 - c_1^*)$. Denoting the average rate of production of $\bar{c}_1$ per cubic centimeter by $\bar{q}_1$ (so that the total amount produced per second throughout the cell is $\frac{4}{3}\pi r^3_0 \bar{q}_1$), we find from a simple "material balance" consideration that

$$\frac{4}{3}\pi r^3_0 \bar{q}_1 - 4\pi r_0 D_1(\bar{c}_1 - c_1^*) = \frac{4}{3}\pi r^3_0 \frac{d\bar{c}_1}{dt}. \tag{2}$$

A similar equation holds for $\bar{c}_2$ with subscripts 1 replaced by 2 everywhere.

To determine c_1^*, we have the boundary condition

$$h_1(c_1^* - c_{01}) = \frac{D_1(\bar{c}_1 - c_1^*)}{r_0} \tag{3}$$

where c_{01} is the external concentration of c_1 and is assumed to be constant. Solving for c_1^*,

$$c_1^* = \frac{D_1 \bar{c}_1 + r_0 h_1 c_{01}}{r_0 h_1 + D_1}. \tag{4}$$

If we substitute in equation (2) the values for $\bar{q}_1$ and c_1^* given in equations (1) and (4), we finally arrive at the pair of ordinary equations

$$\begin{aligned} \frac{d\bar{c}_1}{dt} &= \left(A_{11} - \frac{3 h_1 D_1}{r_0(r_0 h_1 + D_1)}\right)\bar{c}_1 + A_{12}\bar{c}_2 + \frac{3 h_1 D_1}{r_0(r_0 h_1 + D_1)} c_{01} \\ \frac{d\bar{c}_2}{dt} &= A_{21}\bar{c}_2 + \left(A_{22} - \frac{3 h_2 D_2}{r_0(r_0 h_2 + D_2)}\right)\bar{c}_2 + \frac{3 h_2 D_2}{r_0(r_0 h_2 + D_2)} c_{02}. \end{aligned} \tag{5}$$

The solution of a set of equations of this sort is perfectly straightforward (see, e.g., Rashevsky, 1938b). The concentrations $\bar{c}_1$ and $\bar{c}_2$ are found to be essentially exponential functions of the time of the form

$$\bar{c}_i = \alpha_i \, e^{\Lambda t} + \beta_i$$

where α_i and β_i are constants and Λ is given by

$$\Lambda = \tfrac{1}{2}(A_{11} + A_{22}) - \frac{m^2_1 \, D_1 + m^2_2 \, D_2}{2}$$

$$\pm \sqrt{\tfrac{1}{4}[(A_{11} - A_{22}) - (m^2_1 \, D_1 - m^2_2 \, D_2)]^2 + A_{12} \, A_{21}} \, . \tag{6}$$

The symbol m^2_i stands for the quantity $\dfrac{3 \, h_i}{r_0 (D_i + r_0 \, h_i)}$.

Equation (6), which defines the period of oscillation of the concentrations, is entirely general. If the simplifying assumption introduced in (A) is made again, i.e., $\dfrac{h_1}{D_1} = \dfrac{h_2}{D_2}$, we find that $m^2_1 = m^2_2 = m^2$, and so

$$\Lambda = \tfrac{1}{2}(A_{11} + A_{22}) - \frac{m^2}{2}(D_1 + D_2) \pm (D_1 - D_2)$$

$$\times \sqrt{[\frac{m^2}{2} - (A_{11} - A_{22})/2(D_1 - D_2)]^2 + A_{12} \, A_{21}/(D_1 - D_2)^2} \tag{7}$$

which is formally the same as equation (34) (A).

In the rigorous treatment, the quantities m^2 were determined as solutions of the equation

$$\tan m \, r_0 = \frac{D_1}{D_1 - r_0 \, h_1} m \, r_0 \, , \tag{8}$$

whereas in this case

$$m^2 = \frac{3 \, h_1}{r_0 (D_1 + r_0 \, h_1)} . \tag{9}$$

That the first non-zero root of (8) (corresponding to the first harmonic) is of the same order as the m^2 given in (9) may be seen by considering two limiting cases. First, when $D_1 > > r_0 \, h_1$, as seen in (A), the first non-zero root of (8) is

$$m^2 \cong \frac{3 \, h_1}{D_1 \, r_0} ,$$

which result also follows directly from (9); and second, when $D_1 << r_0 h_1$, (8) becomes approximately

$$\tan m r_0 \cong 0$$

and so

$$m \cong \frac{\pi}{r_0}, \quad m^2 \cong \frac{\pi^2}{r^2{}_0},$$

while (9) gives in this case

$$m^2 \cong \frac{3}{r^2{}_0},$$

which is about 1/3 the above value. For intermediate values of D we should expect better agreement between the two results, since the two are identical for large D.

We have thus shown that the period of oscillation of concentrations predicted by the use of this simplified method agrees very well with the period of the first harmonic of the rigorous solution (A), and thus checks the correctness of the previous solution. Furthermore, the approximate method has enabled us (Eq. 6) to determine the period of oscillation when $\frac{h_1}{D_1} \neq \frac{h_2}{D_2}$, a problem which could not be solved rigorously.

The writer is glad to acknowledge his indebtedness to Professor N. Rashevsky for having pointed out to him the applicability of this method to the case at hand.

The preceding results may be improved by doubling the value used here for the average concentration gradient, in accordance with Rashevsky's considerations in a more recent paper (*Bull. Math. Biophysics*, **1**, 23-30, 1939). This modification changes the definition of m^2 so that (9) becomes $m^2 = 6h_1/r_0(2D_1 + r_0 h_1)$ and it makes the numerical agreement with the rigorous result better, although it leaves the general result unchanged.

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THE MECHANISM OF CELL DIVISION

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The recently developed approximation method for treating problems of cell biophysics is generalized and corrected in some points. The equations of elongation of a dividing cell of any shape are given for the most general case of finite permeability as well as of finite internal and external diffusion coefficients.

In the Appendix to our book (Rashevsky, 1938a) we have developed a general approximation method for treating problems of cell deformation under the influence of diffusion. The method while only approximate has the advantage of generality, applying to any elongated shapes without restrictions to an analytically definable boundary surface. At the same time it leads to a very simple and short way of treating such problems, for which an exact mathematical treatment requires a rather involved procedures. H. D. Landahl (1939) has applied this method to the problem of cell respiration and has obtained in a much simpler way the same results which he found previously (Landahl, (1937) by the more elaborate old method. Also A. Weinberg (1939) obtains by this method essentially the same results concerning periodical reactions, as those which are given by the much more elaborate exact method (Weinberg, 1938).

A comparison of the equations for the rate of elongation of a dividing cell, obtained in the Appendix (Rashevsky 1938a), to those obtained in a particular case exactly has been made by G. Young (1939), who worked out the exact expression for an ellipsoid of revolution. This comparison again shows the applicability of the approximate method. The differences found are of no practical consequence, since no dividing cell has a regular shape, and the application to such a cell of formulae which hold *exactly* for an ellipsoid only would be likely to involve as large an error as that by which the approximate equations differ from the exact ones.

In the original exposition of the method given in the Appendix to our book (1938a) we have for sake of simplicity considered the elongation of the cell only in a very special case, namely when both the permeability h and the external diffusion coefficient D_e are infinite, although the diffusion problem was treated for the more general case of finite h and D_i (Rashevsky, 1938a, p. 317). As has been shown by G. Young (1939), in the case of $h = D_e = \infty$ however, we should obtain a zero elongation, since c is constant along the surface. The error committed by us lies in the discussion on p. 308 (Rashevsky, 1938a), where the force appears as a small difference of two quantities. The use of Betti's theorem (Love, 1906, p. 172; Young, 1939), combined with our approximate method for determining the distribution of concentrations, leads to a much more straightforward derivation of the elongation equation and avoids the above mentioned doubtful argument on p. 308 (Rashevsky, 1938a).

Betti's theorem, applied to a plastic body (Young, 1939), gives for the average rate of elongation of a body of *any* shape of volume V in the direction of the z-axis:

$$\frac{1}{a}\frac{d\,a}{d\,t} = \frac{1}{3\,\eta\,V}\iiint_V \left[z\,Z - \tfrac{1}{2}\,(y\,Y + x\,X)\right]d\,V + \frac{1}{3\,\eta\,V}\iint_S \left[Z_\nu\,z - \tfrac{1}{2}\,(X_\nu\,x + Y_\nu\,y)\right]d\,S$$

where X, Y and Z are the components of the force per unit volume and X_ν, Y_ν and Z_ν are the components of any surface force. The triple integral is extended over the whole volume of the body, the double integral over the surface.

If X, Y, Z are derived from a potential, so that (Rashevsky, 1938a, Chapt. VII, VIII, IX):

$$F = -\frac{RT\mu}{M}\,\mathrm{grad}\,c$$

then as is shown by G. Young (1939), the volume integral transforms into a surface integral of the form:

$$-\frac{RT\mu}{M}\iint_S \left\{z\cos(\nu, z) - \tfrac{1}{2}\left[x\cos(\nu x) + y\cos(\nu, y)\right]\right\}d\,S\,.$$

Therefore we have for the average rate of elongation for a body of any shape exactly:

$$\frac{1}{a}\frac{da}{dt} = -\frac{RT}{3M\eta V}\,\mu J + \frac{1}{3\eta V}\,T \tag{1}$$

where, taking z as the direction of elongation:

$$J = \iint c\left\{z\cos(\nu z) - \tfrac{1}{2}\left[x\cos(\nu x) + y\cos(\nu y)\right]\right\}d\,S \tag{2}$$

and

$$T = \iint \left[Z_\nu z - \tfrac{1}{2}\,(X_\nu x + Y_\nu y)\right]dS \tag{3}$$

X_ν, Y_ν, Z_ν being the components of the force $\frac{RT}{M}\,(c_i - c_e)$ at the membrane. For $h = D_e = \infty$, $(c_e - c_i) = 0$ and c is constant along the surface, which makes both J and T vanish. It is therefore indicated to study the more general case, where D_i, h and D_e are all finite. We shall then substitute the approximate value of c at the surface into (1), and thus obtain an approximate expression for the rate of elongation.

In case of a finite D_e the average concentration at the membrane just outside the cell is no longer equal to c_0. We shall denote it by c'_1 for the "ends" of the oblong cell and by c'_2 for its "sides". The average diffusion flows just outside the cell membrane per cm^2 are proportional to $c'_1 - c_0$ and $c'_2 - c_0$ respectively, and to D_e. Denoting the coefficient of proportionately by $1/\delta$ we have for these flows:

$$\frac{D_e}{\delta}(c'_1 - c_0) \text{ and } \frac{D_e}{\delta}(c'_2 - c_0). \tag{4}$$

δ has the dimension of a length and represents a sort of average distance from the cell, at which the external concentration practically becomes equal to c_0. δ is of the order of magnitude of the cell size, but the exact relationship will vary with the details of the cell forms.

At this point we shall also make a slight improvement of the treatment originally presented (Rashevsky, 1938, Appendix). For a not too irregularly varying concentration inside of the cell, the former will have an extremum in the middle, while the average value $\bar{c}$ will be about half-way between the middle and the periphery. Therefore in expressions (48) of the Appendix of our book it is better to use $\frac{1}{2}a$ and $\frac{1}{2}b$ instead of a and b. This does not alter the shape of the final equations, but improves the numerical values of the coefficients. In fact, if we calculate $\bar{c}$ for a spherical cell by averaging the exact expression (Rashevsky, 1938a, Chapt. II, equ. 22), we shall find, for $D_e = \infty$, an expression of the same form as equ. (54) of the Appendix, except that the coefficient of $q\, a^2/D_i$ turns out to be *1/15* instead of *2/9* while the coefficient of $q\, a/h$ is *2/9* instead of *1/3*. The above proposed improvement makes this coefficient in the approximate formula equal to *1/9* leaving the coefficient of aq/h equal to *2/9*, as against *1/3* in the exact expression.

For the stationary state our fundamental equations become now, by the same line of argument as used before (Rashevsky, 1938a, Appendix)

$$D_i(\bar{c} - c_1) = \tfrac{1}{2}\, ah(c_1 - c'_1) \tag{5}$$

$$D_i(\bar{c} - c_2) = \tfrac{1}{2}\, bh(c_2 - c'_2) \tag{6}$$

$$\frac{2D_i}{a}(\bar{c} - c_1) = \frac{D_e}{\delta}(c'_1 - c_0) \tag{7}$$

$$\frac{2D_i}{b}(\bar{c}-c_2)=\frac{D_e}{\delta}(c'_2-c_0) \tag{8}$$

$$D_i\left[\frac{b^2}{a}(\bar{c}-c_1)+2a(\bar{c}-c_2)\right]=\frac{1}{3}ab^2q\,. \tag{9}$$

Equ. (5) and (7) give, eliminating c'_1:

$$c_1=\frac{2(D_iD_e+\delta D_ih)\,\bar{c}+ahD_ec_0}{2D_iD_e+2\delta D_ih+ahD_e}\,. \tag{10}$$

Similarly from (6) and (8):

$$c_2=\frac{2(D_iD_e+\delta D_ih)\,\bar{c}+bhD_ec_0}{2D_iD_e+2\delta D_ih+bhD_e}\,. \tag{11}$$

For $D_e=\infty$, (10) and (11) are of the same form as (52) of the Appendix, except for the correction by the factor 1/2, as should be the case.

From (10) and (11) we have:

$$\begin{aligned}\bar{c}-c_1&=\frac{ahD_e(\bar{c}-c_0)}{2D_iD_e+2\delta D_ih+ahD_e}\\ \bar{c}-c_2&=\frac{bhD_e(\bar{c}-c_0)}{2D_iD_e+2\delta D_ih+bhD_e}\,.\end{aligned} \tag{12}$$

Substituting (12) into (9) we find:

$$\bar{c}=c_0+\frac{abq}{3hD_iD_e}\times \frac{(2D_iD_e+2\delta D_ih+ahD_e)\,(2D_iD_e+2\delta D_ih+bhD_e)}{2(2D_iD_e+2\delta D_ih+ahD_e)\,a+(2D_iD_e+2\delta D_ih+bhD_e)\,b}\,. \tag{13}$$

For a sphere ($a=b$) this gives:

$$\bar{c}=c_0+\frac{2}{9}\frac{aq}{h}+\frac{1}{9}\frac{a^2q}{D_i}+\frac{2}{9}\frac{a\delta q}{D_e}\,; \tag{14}$$

with $\delta \propto a$ this is of the right form.

From (10) and (11) we have:

$$c_2-c_1=\frac{2(D_iD_e+\delta D_ih)\,hD_e\,(a-b)\,(\bar{c}-c_0)}{(2D_iD_e+2\delta D_ih+ahD_e)\,(2D_iD_e+2\delta D_ih+bhD_e)}\,. \tag{15}$$

Introducing (13) into (15):

$$c_2 - c_1 = \frac{abq}{3} \times \frac{2(D_e + \delta h)(a - b)}{2(2D_iD_e + 2\delta D_ih + ahD_e)a + (2D_iD_e + 2\delta D_ih + bhD_e)b} \,. \tag{16}$$

For $h = \infty$, (15) and (16) reduce to

$$c_2 - c_1 = \frac{2\delta D_iD_e}{(2\delta D_i + aD_e)(2\delta D_i + bD_e)}(a - b)(\bar{c} - c_0) \tag{15'}$$

and

$$c_2 - c_1 = \frac{abq}{3} \frac{2\delta(a - b)}{2(2\delta D_i + 2aD_e)a + (2\delta D_i + bD_e)b} \,. \tag{16'}$$

From (5) and (12) we have:

$$\begin{aligned} c_1 - c'_1 &= \frac{2D_iD_e}{2D_iD_e + 2\delta D_ih + ahD_e}(\bar{c} - c_0) \\ c_2 - c'_2 &= \frac{2D_iD_e}{2D_iD_e + 2\delta D_ih + bhD_e}(\bar{c} - c_0) \,. \end{aligned} \tag{17}$$

For $h = \infty$, $c_1 - c'_1 = c_2 - c'_2 = 0$ as should be the case.

Now we may calculate J and T. On the "sides" $\cos(\nu, z) = 0$, while $x \cos(\nu, x) + y \cos(\nu, y) = b$. Hence for the sides the contribution to J is

$$-c_2 \times \tfrac{1}{2} b \times 2\pi b \times 2a = -Vc_2 \,. \tag{18}$$

In a similar way we find that the contribution of the "ends" to J is Vc_1; hence

$$J = V(c_1 - c_2). \tag{19}$$

In calculating T we have

$$X_\nu x + Y_\nu y = \frac{RT}{M} b(c_2 - c'_2)$$

while

$$Z_\nu z = \frac{RT}{M} a(c_1 - c'_1).$$

Therefore

$$T = V\frac{RT}{M}[(c_1 - c'_1) - (c_2 - c'_2)] \,. \tag{20}$$

Introducing (19) and (20) into (1) and substituting into that (15) and (17) we find:

$$\frac{1}{a}\frac{da}{dt}=\frac{2RT}{3M\eta}$$

$$\times\frac{(\mu-1)D_iD_e^2h+\delta D_iD_eh^2\mu}{(2D_iD_e+2\delta D_ih+ahD_e)(2D_i D_e+2\delta D_ih+bhD_e)} \tag{21}$$

$$\times(a-b)(c-\bar{c_0}).$$

For $a=b$ the force and da/dt vanish, as should be the case.

For $q>0$, $\bar{c}-c_0>0$; also $a-b>0$, $(\mu-1)<0$ always. Hence, for sufficiently small $\delta \backsim a \backsim b$, $da/dt<0$ for $q>0$. If however $\delta \backsim a \backsim b$ is sufficienty large, $da/dt>0$ for $q>0$. This agrees with Chapt. IX, MB. To insure positivity of da/dt we must have

$$\delta>\frac{1-\mu}{\mu}\ \frac{D_\epsilon}{h}\backsim 10^{-3}\,cm\,. \tag{22}$$

For $h=\infty$, D_i, D_e finite, (21) reduces to

$$\frac{1}{a}\frac{da}{dt}=\frac{2RT\mu}{3M\eta}\,\frac{\delta D_iD_e}{(2\delta D_i+aD_e)(2\delta D_i+bD_e)}\,(a-b)(\bar{c}-c_0)\,. \tag{23}$$

For $h=\infty$, D_i, D_e finite, (13) reduces to

$$\bar{c}-c_0=\frac{abq}{3D_iD_e}\,\frac{(2\delta D_i+aD_e)(2\delta D_i+bD_e)}{2(2\delta D_i+aD_e)a+(2\delta D_i+bD_e)b}\,. \tag{24}$$

Substituting (24) into (23) we have:

$$\frac{1}{a}\frac{da}{dt}=\frac{2}{9}\,\frac{RT\,ab\,q\mu}{M\eta}\,\frac{(a-b)\delta}{2(2\delta D_i+aD_e)a+(2\delta D_i+bD_e)b}\,. \tag{25}$$

Putting $\delta=b$, (25) becomes:

$$\frac{1}{a}\frac{da}{dt}=\frac{2RT\,q\mu}{9M\eta}\,\frac{(a-b)ab^2}{2(2bD_i+aD_e)a+(2D_i+D_e)b^2}\,. \tag{26}$$

For $a>>b$ this gives:

$$\frac{1}{a}\frac{da}{dt}=\frac{RT\,q\mu}{9M\eta D_e}\,b^2$$

a form to which equ. (22) of the Appendix (Rashevsky, 1938a) reduces also for $a>>b$.

G. Young, 1939, p. 31) makes a comparison of equ. (26) with his equ. (50), which holds exactly for an ellipsoid. The two equations are in substantial agreement, especially over the range of elongations which alone comes into consideration practically.

Since no way has been found yet to integrate *exactly* the diffusion equation for any other shape than the sphere for the case of a finite h, equ. (21) may be used as an approximation in this general case.

Adding to the right-hand side of (25) the effect of the surface tension (Rashevsky, 1938a, p. 311), we obtain

$$\frac{1}{a}\frac{da}{dt} = \frac{2RT\,ab\,q\mu}{9M\eta}\,\frac{(a-b)\delta}{2(2\delta D_i + aD_e)a + (2\delta D_i + bD_e)b} - \frac{1}{3\eta}\,\frac{a-b}{ab}\,\gamma \,. \qquad (27)$$

Requiring $da/dt = 0$, and making $a = b = \delta$, we find from (27) as the critical radius of a sphere below which for any elongation $da/dt < 0$, that is below which it will not elongate

$$a^* = \sqrt[3]{\frac{9M(2D_i + D_e)\gamma}{2RT\mu q}} \qquad (28)$$

This is in better agreement with equ. (34) Chapt. VIII (Rashevsky, 1938) than equ. (34) of the Appendix, because in (34) Chapt. VIII $\overline{D}$ must become infinite with $D_e = \infty$. Equ. (28) requires that the size of a cell should vary as $q^{-1/3}$. Since the "effective" q is proportional to the oxygen consumption (Rashevsky, 1938, Chapt. X), we can check the above relation experimentally. A survey of available data shows that the required relation is approximately satisfied over a rather wide range of values of q. (Rashevsky, 1938c).

As has been pointed out, for sufficiently large elongations equ. (26) reduces to that used before (Rashevsky, 1938a, Appendix). The latter was compared with experimental data on the elongation of a dividing nucleus, observed by K. Belar, and found to represent those data satisfactorily (Rashevsky, 1938c).

In the light of the present discussion the results of our recent paper (Rashevsky, 1938b) concerning cellular forms would have to be modified as to details, although the general methodological results remain the same.

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ON THE MECHANICS OF VISCOUS BODIES AND ELONGATION IN ELLIPSOIDAL CELLS

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After deriving some auxiliary equations for the average elongation of a viscous body under the action of forces derived from a potential, the diffusion problem for an ellipsoidal cell with a constant rate of reaction is solved for the case of an infinite permeability. The equation of elongation of such a cell under the influence of diffusion forces is derived, and compared with the approximate expression obtained by N. Rashevsky for any kind of oblong cell. The two equations are in fair agreement. Effects of constant and variable surface tension are studied.

Average rates of strain in a plastic body:

One of the basic problems in the theory of elasticity is to determine the deformation of an elastic body under the action of specified volume and surface forces. The general problem is difficult and in practice solutions are known only for some particular cases. However, certain quantities connected with the deformation can be evaluated readily by means of results due to Betti. For example if $w(xyz)$ denotes the displacement along the z axis of the point of the body originally at (xyz), then the average value throughout the body of $\delta w/\delta z$ is given by a simple integral involving the applied forces. The quantity $\delta w/\delta z$ is the relative elongation, or strain, in the z direction.

Now in the case of incompressible material (Nadai, 1937, p. 421; 1928, p. 467) (Goodier, 1936) there is an analogy between elastic and viscous bodies, in that strains in the first correspond to rates of strain in the second. If $W(xyz)$ is the velocity of displacement in the z direction, then the rate of strain in that direction is given by $e = \delta W/\delta z$. The mean rate of strain in the z direction, defined as

$$\bar{e} = \frac{1}{v} \iiint_{v} e \, d v \,, \tag{1}$$

can be found by employing Betti's formula (Love, p. 172) in connection with the above mentioned analogy. The result is

$$\bar{e} = \frac{1}{3\,\eta\, v} \left[\begin{aligned} &\iiint_{v} \{ z Z - \tfrac{1}{2}(x X + y Y) \} \, d v \\ &+ \iint \{ z Z' - \tfrac{1}{2}(x X' + y Y') \} \, d S \,. \end{aligned} \right] \tag{2}$$

where V is the volume of the body, η is its coefficient of viscosity,

$X\ Y\ Z$ are the components of applied force per unit of volume, and $X'\ Y'\ Z'$ are the components of applied force per unit area on the body surface.

Kinematically the quantity $\bar{e}$ is interpreted as follows: If e had the constant value $\bar{e}$ throughout the body, then the length of z component of a line joining any 2 points of the body would increase according to

$$\frac{d\,l}{d\,t} = l\,\bar{e}. \qquad (3)$$

This expression also holds if the body is a cylinder and e is a function of z alone. More generally, the expression

$$v\,\bar{e} = \iiint_v \frac{\delta W}{\delta z}\,d\,V \qquad (4)$$

may be transformed (Phillips, p. 70) into

$$v\,\bar{e} = \iint_s W \cos(n\,z)\,d\,S\,. \qquad (5)$$

Thus $\bar{e}$ is determined by the shape of the body and the z velocity of each part of its surface; no knowledge of the motion in the body interior is required.

If the body forces derive from a potential the volume integral in (3) may be further simplied. Letting $(X\ Y\ Z) = \operatorname{grad}\Phi$ the integral has terms $J_z = \iiint z \dfrac{\delta \Phi}{\delta z}\,d\,v$, etc. Integrating by parts with respect to z gives

$$J_z = \iint_S \Phi\,z \cos(\eta\,z)\,d\,s - \iiint_v \Phi\,d\,v\,. \qquad (6)$$

In the same way

$$J_x = \iint_s \phi\,x \cos(\eta\,x)\,d\,s - \iiint_v \Phi\,d\,v\,, \qquad (7)$$

and similarly for J_y. Hence the total integral is

$$J = J_z - \tfrac{1}{2}(J_x + J_y) = \iint_s \Phi\,[z \cos(\eta\,z) - \tfrac{1}{2}\{x \cos(\eta\,x)$$
$$+ y \cos(\eta\,y)\}]\,d\,S\,. \qquad (8)$$

This is seen, upon comparing with the surface integral term in (2), to be the same as if a pressure $-\Phi$ were acting normally over the body surface. This is related to the fact (Love, p. 217) that the effect of a system of volume forces acting upon an elastic body can always be duplicated by a set of surface forces.

If Φ is constant on S then (8) becomes

$$J = \Phi \iint\limits_S [z \cos(\eta z) - \tfrac{1}{2}\{x \cos(\eta x) + y \cos(\eta y)\}]\, d\, S\,. \qquad (9)$$

which vanishes identically. This may be seen by considering that $\iint z \cos(\eta z)\ d\,S = V$, and hence that the integral (9) is essentially $V - \frac{1}{2}(V + V)$.

Hence a constant surface pressure, or a set of volume forces deriving from a potential which is constant on S, gives zero average elongation in any direction.

Diffusion in an ellipsoid:

Previous studies of diffusion processes in cells have for the most part been confined to spherical or nearly spherical shapes. While this may suffice for many cells in their normal or resting states, in which they are nearly spherical, it is not adequate for other important cases. In particular the phenomena of cell division involves changes in shape which carry the cell well away from spherical form.

N. Rashevsky (1938, Appendix) has recently given an approximate method of evaluating a number of quantities concerned in the diffusion process for a rather wide class of elongated cell shapes, such as cylinders and ellipsoids; and it is of interest to have some more exact results available for comparison.

The next simplest shape after a sphere is an ellipsoid of revolution, and this will be treated in what follows, the only approximation being in the assumption that the cell membrane offers no resistance to the passage of the diffusing substance. The results thus obtained are found to agree fairly well with those of Rashevsky and hence afford a certain degree of substantiation of his general method.

Attention will be restricted to a prolate (elongated) ellipsoid of revolution inside of which the dissolved substance is being produced at the constant rate q per unit of volume. Let D represent the coefficient of diffusion and c_0 the concentration of the dissolved substance at great distances, and let the subscripts "i" and "e" refer respectively to the regions internal and external to the ellipsoid. Denote the ellipsoid surface by S. Then the equations to be satisfied are

$$\left.\begin{aligned} \nabla^2 c_i &= 2\,k\,, \\ 2\,k &= -q/D_i\,, \end{aligned}\right\} \qquad (10)$$

$$\left.\begin{aligned} \nabla^2 c_e &= 0\,, \\ c_e &\to c_0 \text{ at } \infty\,, \end{aligned}\right\} \qquad (11)$$

$$c_i = c_e \text{ on } S\,, \qquad (12)$$

$$D_i \frac{\delta c_i}{\delta \eta} = D_e \frac{\delta c_e}{\delta \eta} \text{ on } S. \tag{13}$$

Taking the z direction along the axis of rotation a suitable system of co-ordinates (MacRobert, p. 198; Young and Reiner, 1937) is given by

$$\left.\begin{aligned} x &= \sqrt{r^2 - f^2} \sin\theta \cos\phi, \\ y &= \sqrt{r^2 - f^2} \sin\theta \sin\phi, \\ z &= r\cos\theta, \end{aligned}\right\} \tag{14}$$

The foci of the ellipsoid are at $(0, 0, \pm f)$, and the semi-major and semi-minor axes will be denoted respectively by a and $b = \sqrt{a^2 - f^2}$.

A special solution of (10) is obviously

$$k z^2 = k r^2 \cos^2\theta, \tag{15}$$

to which may be added any solution of $\nabla^2 c_i = 0$. Thus

$$c_i = k r^2 \cos^2\theta + \sum_0^\infty A_n P_n\left(\frac{r}{f}\right) P_n(\cos\theta). \tag{16}$$

Similarly the solution of (11) is

$$c_e = c_0 + \sum_0^\infty B_n Q_n\left(\frac{r}{f}\right) P_n(\cos\theta). \tag{17}$$

Herein P_n and Q_n are the Legendre functions of the first and second kind. Since c_e and c_i are even functions of z it is seen at once that $A_n = B_n = 0$ for n odd.

Expression (15) may be written as

$$k r^2 \left[\frac{2}{3} P_2(\cos\theta) + \frac{1}{3} P_0(\cos\theta)\right]. \tag{18}$$

The boundary condition (12) at the ellipsoid surface ($r = a$) then gives, upon equating coefficients of $P_n(\cos\theta)$,

$$\left.\begin{aligned} &\frac{k a^2}{3} + A_0 = C_0 + B_0 Q_0\left(\frac{a}{f}\right), \\ &\frac{2 k a^2}{3} + A_2 P_2\left(\frac{a}{f}\right) = B_2 Q_2\left(\frac{a}{f}\right), \\ &A_n P_n\left(\frac{a}{f}\right) = B_n Q_n\left(\frac{a}{f}\right) \qquad \text{for } n > 2. \end{aligned}\right\} \tag{19}$$

The boundary condition (13) is equivalent to

$$D_i \frac{\delta c_i}{\delta r} = D_e \frac{\delta c_e}{\delta r} \text{ at } r = a \,, \tag{20}$$

which gives

$$\left.\begin{aligned} &\frac{2}{3} k a f = \frac{D_e}{D_i} B_0 Q'_0\left(\frac{a}{f}\right), \\ &\frac{4}{3} k a f + A_2 P'_2\left(\frac{a}{f}\right) = \frac{D_e}{D_i} B_2 Q'_2\left(\frac{a}{f}\right), \\ &A_n P'_n\left(\frac{a}{f}\right) = \frac{D_e}{D_i} B_n Q'_n\left(\frac{a}{f}\right) \quad \text{for } n > 2 \,. \end{aligned}\right\} \tag{21}$$

From the last relations of (19) and (21) it follows that in general $A_n = B_n = 0$ for $n > 2$. Solving for the remaining coefficients gives

$$\begin{aligned} A_0 &= c_0 - \frac{1}{3} k a^2 + \frac{2}{3} k a f \frac{D_i}{D_e} \frac{Q_0}{Q'_0} \,; \\ B_0 &= \frac{2}{3} k a f \frac{D_i}{D_e} \frac{1}{Q'_0} \,; \\ A_2 &= \frac{2}{3} k a \frac{a D_e Q'_2 - 2 f D_i Q_2}{D_i P'_2 Q_2 - D_e P_2 Q'_2} \,; \\ B_2 &= \frac{2}{3} k a f \frac{D_i}{D_i P'_2 Q_2 - D_e P_2 Q'_2} \,; \end{aligned} \tag{22}$$

where the omitted arguments of the P and Q functions are all a/f. Thus the solution of the diffusion problem is

$$\begin{aligned} c_e &= c_0 + B_0 Q_0\left(\frac{r}{f}\right) + B_2 Q_2\left(\frac{r}{f}\right) P_2(\cos\theta) \,; \\ c_i &= k r^2 \cos^2\theta + A_0 + A_2 P_2\left(\frac{r}{f}\right) P_2(\cos\theta) \,; \end{aligned} \tag{23}$$

with the coefficients given by (22).

Average concentration inside cell:

One of the quantities considered by Rashevsky in his treatment of non-spherical cells is the average concentration of the diffusing substance inside the cell. For purposes of comparison this quantity will now be evaluated for an ellipsoid; namely

$$\bar{c} = \frac{1}{v} \iiint_v c_i \, d\, v \,. \tag{24}$$

In ellipsoidal co-ordinates the volume element is

$$d\, v = (r^2 - f^2 \cos^2 \theta) \sin \theta \, dr \, d\, \theta \, d\, \phi \,, \tag{25}$$

and the range of integration is on ϕ from 0 to $2\,\pi$, on θ from 0 to π, and on r from f to a. Omitting details of the integration, the result is

$$\bar{c} = A_0 + \frac{1}{5}\,(k\, a^2 - A_2) \,. \tag{26}$$

For the case $D_e = \infty$ (22) reduces to

$$\begin{aligned} A_0 &= C_0 - \frac{1}{3} k\, a^2 \,, \\ A_2 &= -\frac{2}{3} k\, a^2 / P_2\left(\frac{a}{f}\right), \\ B_0 &= B_2 = 0 \,. \end{aligned} \tag{27}$$

Substituting in (26) and simplifying gives

$$\bar{c} - c_0 = \frac{q}{5\, D_i} \, \frac{a^2\, b^2}{2\, a^2 + b^2} \,; \tag{28}$$

which should be compared with Rashevsky's expression (Rashevsky, 1938, equ. 24), in which we must make $D_e = \infty$,

$$\bar{c} = c_0 + \frac{q}{3\, D_i} \, \frac{\bar{a}^2\, \bar{b}^2}{2\, \bar{a}^2 + \bar{b}^2} \,. \tag{29}$$

His $\bar{a}$ and $\bar{b}$ denote the half-length and the radius of a "best-fitting" cylinder of the same volume as the body. If these are chosen so that $\bar{a} : \bar{b} = a : b$ then (29) becomes

$$\bar{c} - \bar{c}_0 = 0.26 \, \frac{q}{D} \, \frac{a^2\, b^2}{2\, a^2 + b^2} \tag{30}$$

which is the same order of magnitude as (28) but about 25% larger.

Mechanical effect of volume diffusion forces:

A substance diffusing through a stationary material exerts on the latter a drag force F proportional to the concentration gradient,

$$F = \alpha \nabla c$$
$$\alpha = -R\,T\,\mu/M\,, \tag{31}$$

where M is the molecular weight of the diffusing substance, and R is the Boltzman gas constant. To conform with the particular picture of the structures of the cell used by Rashevsky (1938; chap. viii), we introduce the indefinite factor $\mu \backsim 1$. Further detailed studies of the effect of cytoplasmic structure on the mechanical properties of the cell may either justify the omission of μ, or a general modification of (31).

If then diffusion is taking place in a body we should expect the latter to be deformed by these forces. Regarding a cell as a viscous body (Rashevsky, 1938, p. 130) we can from the above results determine the average rate of elongation of an ellipsoidal cell under the influence of the internal diffusion forces. Since (2) is linear in the force terms, the contributions to $\bar{e}$ of any other kind of forces can be calculated separately and then added thereto.

For a system symmetrical about the z axis the x and y parts of the integral in (2) are equal, so that (8) becomes

$$J = \int\int\int (z\,Z - x\,X)\,d\,v = \int\int \phi[z\cos(n\,z) - x\cos(n\,x)]\,d\,S\,. \tag{32}$$

From (23) it follows that on the ellipsoidal surface S

$$c_i = \text{constant} + A\cos^2\theta\,, \tag{33}$$

where

$$A = k\,a^2 + \frac{3}{2}A_2\,P_2\left(\frac{a}{f}\right). \tag{34}$$

In ellipsoidal co-ordinates (Young and Reiner, 1937)

$$\cos(n\,z)\,d\,S = b^2 \sin\theta\cos\theta\,d\,\theta\,d\,\phi$$
$$\cos(n\,x)\,d\,S = a\,b\sin^2\theta\cos\phi\,d\,\theta\,d\,\phi\,. \tag{35}$$

Writing $\phi = \alpha\,c_i$, and using (14), (33), and (35) in (32), we find upon evaluating the integral, in which the range of integration is from 0 to 2π on ϕ and from 0 to π on θ,

$$J = \frac{8\,\pi\,\alpha}{15}\,a\,b^2\,A\;; \tag{36}$$

and thus the average rate of elongation along the axis of revolution which would be produced by the volume diffusion forces is, according to (2),

$$\bar{e} = J/3\,\eta\,v = \frac{2\,\alpha\,A}{15\,\eta}. \tag{37}$$

From (22) and (34) the quantity A is found to be

$$A = k\,a\,D_i \frac{a\,P'_2 - 2\,f\,P_2}{D_i\,P'_2 - D_e\,P_2 \dfrac{Q'_2}{Q_2}}\,; \tag{38}$$

where as before the P and Q functions have argument $x = a/f$. From the familiar expression

$$P_2(x) = \tfrac{1}{2}(3\,x^2 - 1)\,, \tag{39}$$

the numerator of the fraction in (38) is simply f; while the denominator may be simplified by using the relation (MacRoberts, p. 114)

$$P_2\,Q'_2 - P'_2\,Q_2 = -1/(x^2 - 1)\,. \tag{40}$$

The result is

$$A = \frac{k\,a\,f\,D_i}{3\dfrac{a}{f}\,(D_i - D_e) + D_e \dfrac{1}{(x_2 - 1)\,Q_2}}. \tag{41}$$

For a nearly spherical shape x becomes large and Q_2 becomes

$$Q_2(x) = \frac{2}{15}\,\frac{1}{x^3} + \cdots\,; \tag{42}$$

and in this case A reduces to

$$A = \frac{2}{3}\,k\,f^2\,\frac{D_i}{2\,D_i + 3\,D_e}. \tag{43}$$

For elongated shapes x tends to unity, and $Q_2(x)$ becomes infinite. However it can be shown that

$$\lim_{x=1}\,(x^2 - 1)\,Q_2(x) = 0\,; \tag{44}$$

so that the second term predominates in the denominator of (41). Then

$$A = k\,a\,f\,\frac{D_i}{D_e}\,(x^2 - 1)\,Q_2(x). \tag{45}$$

Explicitly (MacRobert, p. 114)

$$Q_2(x) = \tfrac{1}{4}\left[(3\,x^2 - 1)\,\log\frac{x+1}{x-1} - 6\,x\right]. \tag{46}$$

Near $x = 1$ the first term of this predominates, so that effectively

$$Q_2 = \frac{3x^2 - 1}{4} \log \frac{x+1}{x-1} = \frac{3x^2-1}{4} \log \frac{(x+1)^2}{x^2-1}$$

$$= \frac{3x^2-1}{4} \left[\log (x+1)^2 - \log (x^2 - 1) \right] . \tag{47}$$

Here the second term predominates leaving

$$Q^2(x) = -\tfrac{1}{2} \log (x^2 - 1) ; \tag{48}$$

and thus we find

$$A = -\frac{k\, D_i}{2\, D_e} b^2 \log \frac{b^2}{a^2} , \tag{49}$$

which vanishes as b goes to zero.

From (10), (31), (37), and (41) it follows that

$$\bar{e} = \frac{2}{45} \frac{R\, T\, q\, \mu}{M\, \eta} \frac{a^2 - b^2}{2\, D_i + m\, D_e} , \tag{50}$$

where

$$m = \frac{2}{3\, x (x^2 - 1) Q_2 (x)} - 2 . \tag{51}$$

By use of formula (46) this may be evaluated for different values of a/b. The result is given in the first two columns of the following table:

a/b	m	t^*	m'
22.4	142	25.4	277
10.0	42	12.3	58
7.1	26	9.3	30
5.1	16	7.15	16
3.6	10	6.1	9
2.4	6	4.3	4.7
1.8	4.6	3.8	3
1.34	3.9	3.5	2.1
1.15	3.3	3.3	1.8
1.07	3.06	3.23	1.65
1.00	3.0	3.2	1.57

The last entry, for $a = b$, comes from (43). As the body elongates the effect of the diffusion forces tends to depend more and more upon the value of D_e alone, the D_i term gradually dropping out.

It may be noted that a fair approximation, up to a equal to about $10\, b$, is given by taking $m = 3\, a/b$.

This should be compared with Rashevsky's approximate expression No. 26 which, with $\bar{a} : \bar{b} = a : b$, is

$$\frac{1}{a}\frac{d\,a}{d\,t} = 0.17\,\frac{R\,T\,q\,\mu}{M\,\eta}\,\frac{(a-b)\,a\,b^2}{D_i\,2\,b\,(2\,a+b)+D_e(2\,a^2+b^2)}\,. \tag{52}$$

In effecting the comparison we write (52) in the form

$$\frac{1}{a}\frac{d\,a}{d\,t} = \frac{2}{45}\,\frac{R\,T\,q\,\mu}{M\,\eta}\,\frac{a^2-b^2}{t^*D_i+m'\,D_e}\,, \tag{53}$$

and calculate t^* and m' for various values of a/b. Explicitly,

$$t^* = .534\,(a+b)\,(2\,a+b)/a\,b\,, \tag{54}$$

and

$$m' = .262\,(2\,a^2+b^2)\,(a+b)/a\,b^2\,. \tag{55}$$

Values of these quantities are given in the 3rd and 4th columns of the above table. If $D_e >> D_i$ then expressions (50) and (53) are inversely proportional to m and to m'; and Rashevsky's value for $\bar{e}$ varies from 190% of (50) for nearly spherical shapes down to 70% for $a = 10\,b$. If $D_i >> D_e$ the expressions are inversely proportional to 2 and to t^*, so that (53) is somewhat less than (50). If $D_i = D_e$ the agreement is still better for shapes not too far from spherical, as is seen by comparing $m+2$ with $m'+t^*$.

Effect of constant surface tension:

Another type of force involved is that of surface tension. A surface tension constant over the cell surface tends to keep it rounded up, and so opposes any elongation. We now calculate this effect for an ellipsoid of revolution.

The principal radii of curvature of such a surface are

$$R_1 = \frac{(a^2-f^2\cos^2\theta)^{3/2}}{a\,b}\,, \tag{56}$$

which is the curvature of a meridian section, and

$$R_2 = \frac{b}{a}\,(a^2-f^2\cos^2\theta)^{1/2}\,. \tag{57}$$

The mean curvature is $K = \frac{1}{R_1}+\frac{1}{R_2}$, and at each point of the body surface a surface tension γ exerts an inward normal pressure equal to $\gamma\,K$. Thus the surface stress in the z direction is $-\gamma\,K\cos\,(n\,z)$; in the x direction it is $-\gamma\,K\cos\,(n\,x)$. The surface integral in (2) accordingly becomes

$$T = -\gamma\iint_s K[z\cos(n\,z) - x\cos(n\,x)]\,d\,S\,. \tag{58}$$

The integral here may be expressed as $Z_1 + Z_2 - X_1 - X_2$, where Z and X refer to the z and x terms in the integrand, and the subscripts 1 and 2 refer to the two terms in K. Thus

$$Z_1 = \int\int \frac{1}{R_1} z \cos(n\,z)\, d\,S, \tag{59}$$

and similarly for the others.

We find

$$Z_1 = 2\,\pi\,a^2\,b^3 \int_0^\pi \frac{\cos^2\theta\,\sin\theta\,d\,\theta}{(a^2 - f^2\cos^2\theta)^{3/2}}, \tag{60}$$

which, with the substitution $x = \cos\theta$, becomes

$$Z_1 = 2\pi \frac{a^2 b^3}{f^3} \int_{-1}^{1} \frac{x^2\,d\,x}{\left(\frac{a^2}{f^2} - x^2\right)^{3/2}} \tag{61}$$

This may be evaluated from a standard table of integrals, e.g. Peirce, integral no. 157.

Proceeding similarly, with the same substitution, Z_2, X_1, and X_2 reduce to forms which can be evaluated from Peirce's nos. 157, 151, 139, and 127. The details are fairly lengthy and will be omitted here. The final result is

$$T = -\pi\,\gamma\,b \left[\begin{array}{l} -2\,b + 3\,\dfrac{a^2\,b}{f^2} \\ -\left(3\,\dfrac{a^4}{f^3} - 4\,\dfrac{a^2}{f}\right) \sin^{-1}\dfrac{f}{a}. \end{array} \right] \tag{62}$$

For a nearly spherical shape, for which f/a is small, we find by expanding $\sin^{-1}\frac{f}{a}$ and $b = a\sqrt{1 - \frac{f^2}{a^2}}$ in powers of f/a, that the bracketed expression in (62) tends to $\frac{16}{15}\frac{f^2}{a}$.

Thus

$$\bar{e} = T/3\,\eta\,V = -\frac{\gamma}{3\,\eta}\,\frac{4}{5}\,\frac{a^2 - b^2}{a^2\,b}; \tag{63}$$

or, since $a \simeq b$,

$$\bar{e} = -\frac{\gamma}{3\,\eta}\,\frac{8}{5}\,\frac{a - b}{a\,b} \tag{64}$$

For very elongated shapes, with $f \simeq a$, the bracket tends to $\pi\,a/2$ and thus

$$\bar{e} = -\frac{\gamma}{3\eta}\frac{3\pi}{8}\frac{1}{b}. \qquad (65)$$

Since $a >> b$ this may be written as

$$\bar{e} = -\frac{\gamma}{3\eta}\frac{3\pi}{8}\frac{a-b}{a\,b}. \qquad (66)$$

If $a = 2\,b$ the arc sine term in (62) drops out and the bracket is equal to a, which gives

$$\bar{e} = -\frac{\gamma}{3\eta}\frac{3}{4}\frac{1}{b} = -\frac{\gamma}{3\eta}\frac{3}{2}\frac{a-b}{a\,b}. \qquad (67)$$

To consider whether $\bar{e}$ can change sign for intermediate eccentricities of the ellipsoid, we first note that the bracket is necessarily positive for $a \geq 2\,b$. It is zero for $f = 0$, and positive for f just greater than zero, as was seen in connection with (63). Hence (for simplicity taking $a = 1$) if it is to have a negative value at all it must vanish for some positive value of f less than $\sqrt{3/4}$ (which corresponds to $a < 2b$). For this to occur there must be a root of the equation

$$\sin^{-1} f = f\sqrt{1-f^2}\,\frac{3-2f^2}{3-4f^2} \qquad (68)$$

between 0 and $\sqrt{3/4}$. Now the derivatives of the expressions on the two sides are respectively

$$\text{(left)} \qquad \frac{1}{\sqrt{1-f^2}} \qquad (69)$$

and

$$\text{(right)} \qquad \frac{9-24f^2+32f^4-16f^6}{9-24f^2+16f^4}\,\frac{1}{\sqrt{1-f^2}}. \qquad (70)$$

On the range $0 < f^2 < 3/4$ expression (70) is positive and greater than (69). Hence the right side of (68) increases faster than the left and, since they are equal at $f = 0$, they cannot again become equal for $f < \sqrt{3/4}$.

Thus the bracket is always positive and the $\bar{e}$ contribution of the surface tension is always negative. This bears out the statement made above that a constant surface tension always opposes elongation.

Rashevsky's approximate expression for the surface tension effect (1938, p. 311) is

$$\frac{1}{a}\frac{d\,a}{d\,t} = -\frac{\gamma}{3\eta}\frac{\bar{a}-\bar{b}}{\bar{a}\,\bar{b}}; \qquad (71)$$

which with $\bar{a} : \bar{b} = a : b$ becomes

$$\frac{1}{a}\frac{d\,a}{d\,t} = -\frac{\gamma}{3\,\eta}\sqrt[3]{\frac{3}{2}}\,\frac{a-b}{a\,b}\,. \tag{72}$$

The above expressions may be summed up in the formula

$$-\frac{\gamma}{3\,\eta}\,\alpha\,\frac{a-b}{a\,b}\,, \tag{73}$$

where the values of α are as follows:

	α : ellipsoid	α : Rashevsky
$a \simeq b$	1.6	1.15
$a = 2\,b$	1.5	1.15
$a >> b$	1.18	1.15

The agreement is seen to be good, Rashevsky's formula merely underestimating the surface tension effect a little for nearly round shapes.

Effect of variable surface tension:

A surface tension which is not constant, but varies from point to point on the surface, is regarded by many physiologists (Wilson, 192-197) as playing an important role in cell deformations. We shall here consider a simple case of this effect.

For simplicity suppose that the variation is merely between poles and equator of the ellipsoid, and that it is given by

$$\gamma = \text{constant} + t_1 \cos^2\theta\,. \tag{74}$$

Consider first the mechanical effect on the body due to the variation in perpendicular pressure on its surface. For this it is necessary only to amend the integral of (58) by inserting a $\cos^2\theta$ factor into the integrand. The procedure is then as before, except that a couple of new integral type forms are needed. These are given by Dwight (1934) as numbers 324.01 and 324.03. The final result for the contribution of this term to $\bar{e}$ is

$$\bar{e} = -\frac{t_1}{4\,\eta}\frac{a}{f^2}\left[\begin{array}{l}\dfrac{27}{4}\dfrac{a^2}{f^2} - \dfrac{11}{2} \\ + \dfrac{1}{b\,f}\left(-\dfrac{27}{4}\dfrac{a^4}{f^2} + 8\,a^2 + 2\,b^2\right)\sin^{-1}\dfrac{f}{a}\end{array}\right] \tag{75}$$

For a nearly spherical shape this becomes

$$\bar{e} = -\frac{t_1}{\eta}\frac{4}{15}\frac{a}{b^2} = -\frac{t_1}{\eta}0.27\frac{1}{b}\,; \tag{76}$$

for a = about $2\frac{1}{4}\,b$ it is

$$\bar{e} = -\frac{t_1}{\eta}\,0.42\,\frac{1}{b}\;; \tag{77}$$

while for a very elongated shape

$$\bar{e} = -\frac{t_1}{\eta}\,\frac{5\pi}{32}\,\frac{1}{b} = -\frac{t_1}{\eta}\,0.49\,\frac{1}{b}\,. \tag{78}$$

Thus in general

$$\bar{e} = -\frac{t_1}{\eta}\,\beta\,\frac{1}{b}\,, \tag{79}$$

where apparently β increases from about $\frac{1}{4}$ to $\frac{1}{2}$ as the body elongates from spherical shape. A positive tendency to elongate requires that t_1 be negative; i.e. that γ be greater at the equator than at the poles.

However, the variation in normal pressure is not the only mechanical feature involved. If the surface tension varies over the body there will also be tangential stresses present, since otherwise each surface element would be subjected to a net uncompensated pull. A simple illustration is a body covered by a sheet of rubber which is stretched non-uniformly. To maintain the non-uniform tension in the rubber it is necessary that friction with the body surface provide appropriate tangential stresses. But then the body is also subject to tangential surface stresses; i.e. the non-uniform surface tension gives rise to both normal and tangential stresses on the body.

It might be possible, on the other hand, to have the requisite tangential stresses on the rubber supplied from the outside; in which case they would not be transmitted to the inner body. In general they may be partially sustained by the inside body and partly by some outside agency. This latter would appear to be the case in actual cells, as illustrated by the experiments of Quincke (Wilson, p. 194) in which attendant streamings are observed both outside and inside the drop.

For purposes of computation let us consider the first case, in which the entire unbalanced tangential surface stress is transmitted to the body inside. It is seen at once that the effect will oppose that of the varying perpendicular pressure, in that a γ higher at the equator gives rise to surface pulls directed toward the equator and hence tending to shorten the body.

In the case of a system of revolution this tangential stress at each point of the body surface is directed toward the equator along the meridian curve and is equal in amount to $d\,\gamma/dl$, where dl is the arc length along the curve measured toward the equator. For an ellipsoid, and with γ given by (74), this turns out to be

$$\frac{d\gamma}{dl} = -\frac{2\,t_1 \cos\theta \sin\theta}{\sqrt{a^2 - f^2 \cos^2\theta}}. \tag{80}$$

Taking into account the angles between the surface tangent and the z and x axes we find the component surface stresses to be

$$Z' = \frac{2\,a\,t_1 \cos\theta \sin^2\theta}{a^2 - f^2\cos^2\theta}$$

$$X' = -\frac{2\,b\,t_1 \cos^2\theta \sin\theta \cos\phi}{a^2 - f^2 \cos^2\theta}. \tag{81}$$

The surface element is

$$dS = b \sin\theta \sqrt{a^2 - f^2\cos^2\theta}\, d\theta\, d\phi. \tag{82}$$

Upon writing out the expressions for $\int\int z\, Z' ds$ and $\int\int x\, X'\, ds$ it is found that they reduce to one of the integrals encountered above, and that the final result is

$$\bar{e} = \frac{t_1}{2\eta} \frac{2a^2 + b^2}{a\,b} \frac{1}{f} \left[-\frac{b}{2f} + \frac{3a^2 b}{4f^3} + \left(\frac{a^2}{f^2} - \frac{3}{4}\frac{a^4}{f^4}\right) \sin^{-1}\frac{f}{a} \right]. \tag{83}$$

For a nearly spherical shape this reduces to

$$\bar{e} = \frac{t_1}{\eta} \frac{2}{5} \frac{1}{b}; \tag{84}$$

at $a = 2\,b$ it is

$$\bar{e} = \frac{t_1}{\eta} \frac{3}{8} \frac{1}{b}; \tag{85}$$

and for long shapes

$$\bar{e} = \frac{t_1}{\eta} \frac{\pi}{8} \frac{1}{b}. \tag{86}$$

Thus the contribution of the tangential stresses is

$$\bar{e} = \frac{t_1}{\eta}\, \alpha_1 \frac{1}{b}, \tag{87}$$

where apparently α_1 is nearly equal to 0.4.

Comparing with (79) shows the opposition of the two types of stresses as mentioned above. It should be noted that one or the other may predominate depending upon the shape of the body. For a nearly spherical shape the tangential stresses predominate so that a net average elongation requires that γ be larger at the poles, while for longer shapes γ must be larger at the equator. The quantities α_1 and β have been evaluated above only at three shapes apiece, but from these it appears that the change in term predominance takes place at about $a = 2b$. This may shed some light on the controversy as to whether γ should be larger at poles or at equator in order to divide a cell (Wilson, p. 197). The presence of the constant term in (74) always acts to reduce $\bar{e}$, as seen earlier, and so to oppose elongation. There is thus a variety of possibilities of elongated shapes having average lengthwise equilibrium, in the sense that $\bar{e}$ is zero, under the action of a variable surface tension.

If part of the tangential stress is sustained by the cell exterior, then (87) would be reduced and the normal pressure term (79) would become more dominant.

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MATHEMATICAL BIOPHYSICS OF THE CELL WITH REFERENCE TO THE CONTRACTILITY OF TISSUES AND AMOEBOID MOVEMENTS

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Using a recently developed approximation method, the problem of the deformation of a cell under the action of diffusion forces is studied for the general case when the rate of deformation is so rapid that the diffusion state is not quasistationary. The possibilities of configurations with several equilibria, as well as of periodical contractions and expansions of the cell around one of such configurations are shown. The bearing of these results on the theory of tissue contractility and amoeboid movements is discussed.

In our book, "Mathematical Biophysics" (Rashevsky, 1938), hereinafter referred to as MB, we have given and discussed the equations of elongation of a dividing cell, under the influence of "metabolic diffusion forces". We have considered in more detail the case when the elongation is so slow that at each moment the diffusion state may be considered as quasistationary. We have however given also, without discussion, equations for the general case, when the speed of deformation may be arbitrary (MB, p. 315). The general equations have been corrected and amplified in a subsequent paper (Rashevsky, 1939). In the present paper we shall discuss somewhat more at length the case of deformations, which are sufficiently rapid so that the conditions of quasistationarity are not satisfied. In conclusion we shall point out the possible bearing of these cases on several important biological problems.

I.

Instead of equ. (45) p. 315 of MB, we consider the more general equation:

$$\frac{4}{3}\pi ab^2\frac{d\bar{c}}{dt}=\frac{4}{3}\pi ab^2 q$$

$$-4\pi D_i D_e\frac{b^2(D_e+2D_i)+2a(aD_e+2bD_i)}{(aD_e+2bD_i)(D_e+2D_i)}(\bar{c}-c_0), \qquad (1)$$

which is easily obtained by the same argument as equations (5) to (9) of a previous paper (Rashevsky, 1939), by putting $h=\infty$ $\delta=b$ the notations here being the same as there. Putting

$$\bar{c} - c_0 = c \, , \tag{2}$$

equ. (1) may be written:

$$\frac{dc}{dt} = q - \frac{3D_iD_e}{ab^2} \frac{b^2(D_e + 2D_i) + 2(aD_e + 2bD_i)}{(aD_e + 2bD_i)(D_e + 2D_i)} c \, . \tag{3}$$

Instead of equation (47), p. 315 of MB, we have now the improved equation:

$$\frac{1}{a}\frac{da}{dt} = \frac{2RT\mu}{3M\eta} \frac{\delta D_iD_e(a - b)}{(2\delta D_i + aD_e)(2\delta D_i + bD_e)} c \, , \tag{4}$$

in which we have to put $\delta = b$ (Rashevsky, 1939, equ. 23). Adding also to the right hand side of (4) the term $-\gamma(a - b)/3\eta ab$ which expresses the effect of the surface tension (MB, p. 311, equ. 36), we obtain:

$$\frac{1}{a}\frac{da}{dt} = \frac{2RT\mu}{3M\eta} \frac{D_iD_e(a - b)}{(2bD_i + aD_e)(2D_i + D_e)} c - \frac{\gamma}{3\eta} \frac{a - b}{ab} \, . \tag{5}$$

We shall now discuss the simultaneous differential equations (3) and (5).

The requirement

$$\frac{dc}{dt} \geqq 0 \, , \tag{6}$$

introduced into (3), gives:

$$c \leqq \frac{ab^2q}{3D_iD_e} \frac{(aD_e + 2bD_i)(D_e + 2D_i)}{2a(aD_e + 2bD_i) + b^2(D_e + 2D_i)} \, . \tag{7}$$

The equality sign in (7) gives an equation of a line, for which $dc/dt = 0$. Since (MB, Appendix):

$$b^2 = \frac{3V}{4\pi a} \, ; \qquad V = \frac{4}{3}\pi a_0^3 \, ; \qquad a_0 = \left(\frac{3V}{4\pi}\right)^{1/3} \, ; \tag{8}$$

the equation (7) may be written:

$$c = \frac{Vq(D_e + 2D_i)}{4\pi D_iD_e} \frac{D_e a + 2D_i\sqrt{3V/4\pi a}}{2D_e a^2 + 4D_i\sqrt{3Va/4\pi} + 3V(D_e + 2D_i)/4\pi a} \, . \tag{9}$$

For very large values of a, we have:

$$c = \frac{Vq(D_e + 2D_i)}{8\pi D_iD_e} \frac{1}{a} \, . \tag{10}$$

For very small values of a, we have:

$$c = \frac{2q}{3D_e}\sqrt{\frac{3Va}{4\pi}}. \tag{11}$$

From (10) and (11) we see that $c = 0$ for $a = 0$ and for $a = \infty$. The value of c is everywhere positive. From physical considerations it is clear that c should have a maximum for $a = a_0 = \sqrt[3]{3V/4\pi}$, that is, when the cell is spherical (Fig. 1, full line). For $D_e = \infty$ this is actually the case, as can be easily seen. For finite D_e (9) gives a maximum at a point slightly different from a_0. This is due to the approximations introduced by making $\delta = b$ (Rashevsky, 1939) which is not quite exact.

Because of equation (5), the requirement

$$\frac{da}{dt} > 0 \tag{12}$$

leads to

$$c \geqq \frac{M\gamma(2D_i + D_e)}{2RT\mu D_i D_e}\left(\frac{2D_i}{a} + \frac{D_e}{b}\right) \tag{13}$$

for

$$a > b\,;$$

and to

$$c \leqq \frac{M\gamma(2D_i + D_e)}{2RT\mu D_i D_e}\left(\frac{2D_i}{a} + \frac{D_e}{b}\right) \tag{14}$$

for

$$a < b\,.$$

Because of (8), equations (13) and (14) may be written thus:

$$c \geqq \frac{M\gamma(2D_i + D_e)}{2RT\mu D_i D_e}\left(\frac{2D_i}{a} + \frac{D_e}{a_0{}^{3/2}}\sqrt{a}\right) \quad \text{for} \quad a > b\,; \tag{15}$$

and

$$c \leqq \frac{M\gamma(2D_i + D_e)}{2RT\mu D_i D_e}\left(\frac{2D_i}{a} + \frac{D_e}{a_0{}^{3/2}}\sqrt{a}\right) \quad \text{for} \quad a < b\,. \tag{16}$$

For $a = b$ equ. (4) gives always $da/dt = 0$. The equality sign in (15) and (16) gives us an equation of a curve which is infinite for $a = 0$, varying for small values of a like $1/a$; while for larger values of a it varies as $\sqrt{a}$ (Fig. 1, broken line). It has a minimum for

$$a = \left(\frac{4D_i}{D_e}\right)^{2/3} a_0\,. \tag{17}$$

The two lines (9) and (15) may either not intersect at all (Fig. 1) or they may intersect as in Fig. 2 or in Fig. 3.

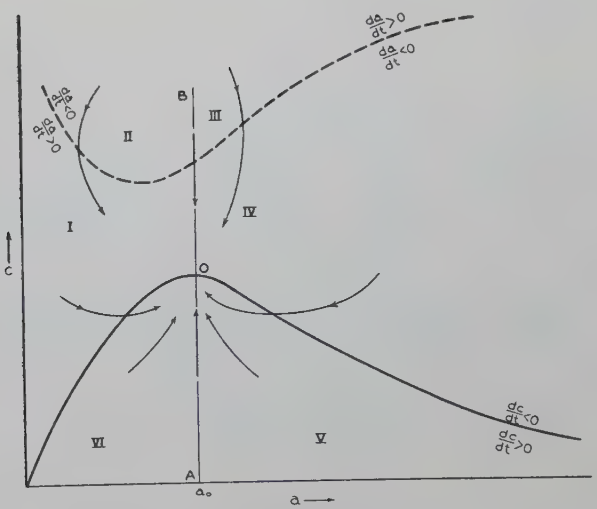

FIGURE 1

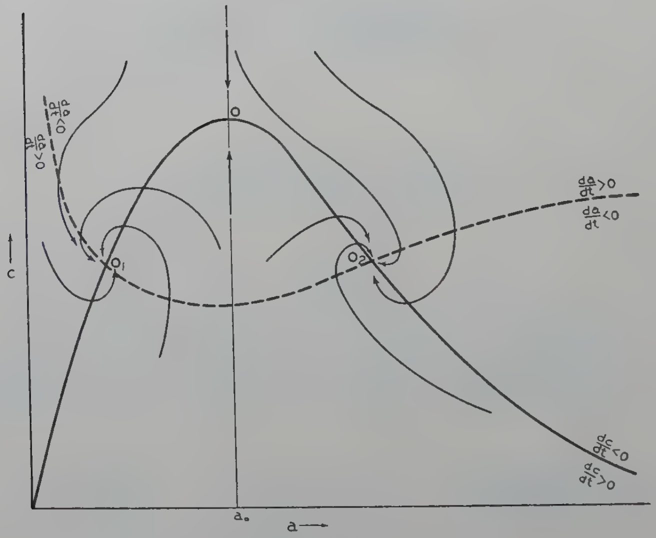

FIGURE 2

The case of Fig. 1 will happen when for a given a_0, and other constants, the value of q is sufficiently small, resulting in a too low concentration $c = \bar{c} - c_0$ at the maximum, which corresponds to a sphere. In this case the two lines (9) and (15), together with the line AB which corresponds to $a = a_0$, divide the quadrant of the a,c — plane into six regions. In region I $dc/dt < 0$ because of (6) and (9), while $da/dt > 0$, because of (12) and (16). Any configuration point

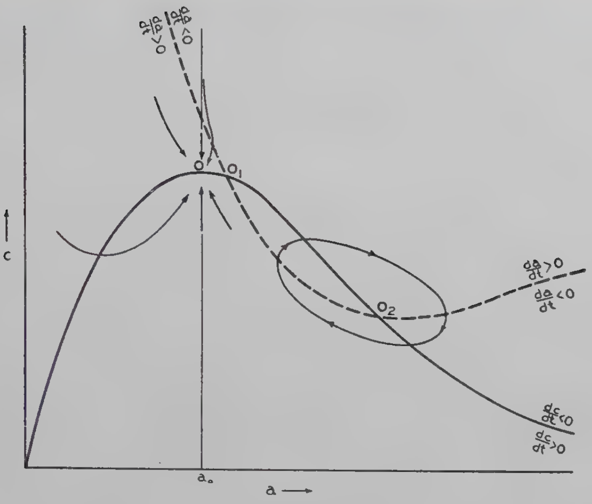

FIGURE 3

in the a,c — plane moves in the direction indicated by the arrow. In region *II* we have $dc/dt < 0$, $da/dt < 0$; the direction of the movement of a configuration point is also indicated by the arrow. In region *III* $da/dt > 0$; $dc/dt < 0$, while in region *IV* $da/dt < 0$ $dc/dt < 0$. A similar survey of the other regions leads us to a distribution of pathways along which the configuration point moves according to equations (3) and (5) as shown on Fig. 1. For any point on AB, $da/dt = 0$. Therefore above the heavy line any such point will move downwards, below it — upwards. All paths converge to the point O, which corresponds to $a = b = a_0$, that is, to a sphere. This is quite clear physically, since for very small values of q the sphere is a stable shape of equilibrium.

A similar analysis of the case represented on Fig. 2 leads to a different distribution of the paths. The point O is now a point of unstable equilibrium. There are now two points O_1 and O_2 of stable equilibrium, towards which the paths converge. The point O_1 corresponds to $a < a_0$, or $a < b$; in other words to a flattened shape. The point O_2 corresponds to $a > a_0$ or $a > b$, that is, to an elongated shape. This happens when, due to a sufficiently large q, the sphere becomes unstable for a given a_0, that is, when a_0 becomes greater than the critical radius a^* given by equ. (28) of a previous paper (Rashevsky, 1939). In this case the metabolic forces begin to elongate the cell. This elongation may proceed either in one direction only, leading to oblong shapes with an eventual division in two; or it may proceed in two directions, leading to flattened shapes, like for instance red blood corpuscles.

From Fig. 2 we see, that while the paths of the configuration points converge towards O_1 and O_2, they do not necessarily approach those points directly. These paths are in general convergent spirals, and represent therefore damped oscillations of c and a around the points O_1 and O_2.

For the situation represented on Fig. 3 a possibility of undamped periodic oscillations exists. In this case both O_1 and O_2 correspond to $a > a_0$. But O_1 is unstable, while O and O_2 are stable. The paths around O_2 may be closed lines, representing undamped oscillations, which of course are not sinusoidal in general. If the case represented on Fig. (3) is actually realised, then a cell would be in a relatively stable equilibrium when spherical. It will require a *finite* external disturbance to elongate it to the length a_1, corresponding to O_1. But if a finite external disturbance brings the cell into a configuration for which $a > a_1$, then the cell will stretch spontaneously further and will oscillate indefinitely, contracting and expanding rhythmically.

The exact analytical determination of the paths of the configuration points presents a rather difficult problem, due to the nonlinearity of equations (3) and (4). We may however study the behaviour of the cell in the immediate neighborhood of the points O, O_1 and O_2, by expanding the functions $v(a,c) = dc/dt$ and $u(a,c) = da/dt$ in the vicinity of the corresponding points. But even then this requires an analytical expression for the coordinates a_1, c_1 and a_2, c_2 of O_1 and O_2, which it is difficult to obtain in an exact closed form. For a general orientation we may use however some rather crude approximations. As *an illustration* we shall use it for the study of the behaviour of the system in the vicinity of O_2 in the case represented on Fig. (3).

That case will occur when the minimum of (15), given by (17), is shifted very much to the right. This happens when $D_i >> D_e$. We shall therefore consider such a case, in which D_e may be neglected as compared with D_i, when the two occur as a sum or difference. Moreover we shall consider the case that a_1 is so far to the right, that instead of (9) we may use in this region the approximate expression (10). The latter now becomes:

$$c = \frac{Vq}{4\pi D_e} \frac{1}{a}, \tag{18}$$

which is the approximate equation of the heavy line of Fig. (3) for large values of a. Subsequently we shall investigate the degree of approximation given by (18).

Equ. (15) now becomes:

$$c = \frac{M\gamma}{RT\mu D_e} \left(\frac{2D_i}{a} + \frac{D_e}{a_0^{3/2}} \sqrt{a}\right). \tag{19}$$

The abscissa a_2 of the point O_2 is obtained by equating the right hand sides of (18) and (19), which gives:

$$\frac{Vq}{4\pi D_e}\frac{1}{a_2} = \frac{M\gamma}{RT\mu D_e}\left(\frac{2D_i}{a_2} + \frac{D_e}{a_0^{3/2}}\sqrt{a_2}\right);$$

or rearranging:

$$\left(\frac{Vq}{8\pi} - \frac{M\gamma D_i}{RT\mu}\right) = \frac{M\gamma D_e}{2RT\mu}\left(\frac{a_2}{a_0}\right)^{3/2}. \qquad (20)$$

In MB, Appendix and a previous paper (Rashevsky, 1939) we have defined the critical radius of a cell as the radius above which the cell elongates spontaneously, for any deformation, no matter how small. We shall call the corresponding volume the critical volume V_c. In the case represented on Fig. (3), $V < V_c$, since between O and O_1 the spherical shape is the stable one, and the cell does not elongate spontaneously at O.

$$V < V_c = \frac{4}{3}\pi a^{*3}; \qquad (21)$$

where a^* is given by equ. (28) of a previous paper (Rashevsky, 1939), namely:

$$a^* = \sqrt[3]{\frac{9M(2D_i + D_e)\gamma}{2RT\mu q}} \qquad (22)$$

Combining (21) with (22) and neglecting D_e, we have

$$V < V_c = \frac{12\pi M D_i\gamma}{RT\mu q}. \qquad (23)$$

Putting

$$\alpha = 3\frac{V}{V_c} - 2, \qquad (24)$$

(20) and (23) give:

$$\left(\frac{a_2}{a_0}\right)^{3/2} = \alpha\frac{D_i}{D_e},$$

or

$$a_2 = a_0\left(\frac{\alpha D_i}{D_e}\right)^{2/3}. \qquad (25)$$

While α may be negative, a_2 is always positive because of the 2/3 power.

Introducing now the value (25) of a_2 into (18), we find the ordinate c_2 of O_2. After some rearrangement this gives:

$$c_2 = \frac{Vq}{4\pi a_0\sqrt[3]{D_e D_i^2\alpha^2}}. \qquad (26)$$

Equation (5) reduces, for $a >> b$, to

$$\frac{da}{dt} = \frac{2RT\mu}{3M\eta} \frac{D_i D_e a^2}{(2bD_i + aD_e)(2D_i + D_e)} c - \frac{\gamma a}{3\eta b}. \tag{27}$$

For $D_i >> D_e$ and for very large values of a, this becomes

$$\frac{da}{dt} = \frac{RT\mu D_e}{6M\eta D_i} \sqrt{\frac{4\eta}{3V}}\, a^{5/2} c - \frac{\gamma}{3\eta} \sqrt{\frac{4\pi}{3V}}\, a^{3/2}. \tag{28}$$

Denote

$$u = \frac{da}{dt}; \quad v = \frac{dc}{dt}. \tag{29}$$

Since, at O_2, $u = O$, we have in the vicinity of O_2

$$u = \frac{da}{dt} = \left(\frac{\partial u}{\partial a}\right)_{O_2} (a - a_2) + \left(\frac{\partial u}{\partial c}\right)_{O_2} (c - c_2), \tag{30}$$

where the subscript indicates that the values of the derivatives are to be taken at O_2, that is, for $a = a_2$, $c = c_2$.

From (28) we have, using (8):

$$\left(\frac{\partial u}{\partial a}\right)_{O_2} = \frac{5RT\mu D_e}{12M\eta D_i a_0^{3/2}} a_2^{3/2} c_2 - \frac{\gamma a_2^{1/2}}{2\eta a_0^{3/2}}. \tag{31}$$

Because of (18), in which we must put now $a = a_2$, $c = c_2$, (31) may be written:

$$\left(\frac{\partial u}{\partial a}\right)_{O_2} = \left(\frac{5RT\mu qV}{48\pi MD_i} - \frac{\gamma}{2}\right) \frac{a_2^{1/2}}{\eta a_0^{3/2}}. \tag{32}$$

Putting:

$$\frac{5}{2} \frac{V}{V_c} - 1 = \beta, \tag{33}$$

(32) may be written, because of (23):

$$\left(\frac{\partial u}{\partial a}\right)_{O_2} = \frac{\beta \gamma a_2^{1/2}}{2\eta a_0^{3/2}}. \tag{34}$$

From (28) and (29) we also have:

$$\left(\frac{\partial u}{\partial c}\right)_{O_2} = \frac{RT\mu D_e}{6M\eta D_i} \sqrt{\frac{4\pi}{3V}}\, a_2^{5/2},$$

which, because of (8) and (25), may be written:

$$\left(\frac{\partial u}{\partial c}\right)_{O_2} = \frac{RT\mu a_0 |\alpha|}{6M\eta} \left(\frac{\alpha D_i}{D_e}\right)^{2/3}, \tag{35}$$

The absolute value $|\alpha|$ of α is taken in order to indicate that (35) is always positive because $a_2 > 0$.

Introducing now (8) into (3), the latter may be written:

$$\frac{dc}{dt} = q - \frac{4\pi D_i D_e}{V(D_e + 2D_i)} \frac{3V(D_e + 2D_i)/4\pi a + 2D_e a^2 + 4D_i \sqrt{3Va/4\pi}}{D_e a + 2D_i \sqrt{3V/4\pi a}} c. \tag{36}$$

For large values of a and for $D_i >> D_e$ this becomes because of (21)

$$v = q - \frac{4\pi D_e}{V} ac. \tag{37}$$

Since at O_2, $v = 0$, therefore in the neighborhood of O_2, we have

$$v = \frac{dc}{dt} = \left(\frac{\partial v}{\partial a}\right)_{O_2} (a - a_2) + \left(\frac{\partial v}{\partial c}\right)_{O_2} (c - c_2). \tag{38}$$

Using (8) and (25) we obtain from (37):

$$\left(\frac{\partial v}{\partial a}\right)_{O_2} = -\frac{q}{a_0} \left(\frac{D_e}{\alpha D_i}\right)^{2/3}; \quad \left(\frac{\partial v}{\partial c}\right)_{O_2} = -\frac{3\sqrt[3]{D_e D^2{}_i \alpha^2}}{a^2{}_0}. \tag{39}$$

Introducing now the notations

$$x = a - a_2; \quad y = c - c_2;$$

$$A_1 = \frac{\beta\gamma a_2{}^{1/2}}{2\eta a_0{}^{3/2}}; \quad A_2 = -\frac{q}{a_0} \left(\frac{D_e}{\alpha D_i}\right)^{2/3};$$

$$B_1 = \frac{RT\mu a_0 |\alpha|^{5/3}}{6M\eta} \left(\frac{D_i}{D_e}\right)^{2/3}; \quad B_2 = -\frac{3\sqrt[3]{D_e D^2{}_i \alpha^2}}{a^2{}_0}; \tag{40}$$

we find from equations (30), (38), (29), (34), (35), and (39):

$$\frac{dx}{dt} = A_1 x + B_1 y.$$

$$\frac{dy}{dt} = A_2 x + B_2 y. \tag{41}$$

The solution of this system of equations is well known (Rashevsky, 1938a). It possesses undamped periodical solutions, if

$$A_1 + B_2 = 0 \tag{42}$$

and

$$A_1B_2 - B_1A_2 > 0\,. \tag{43}$$

Requirement (42) together with (40) gives, after simple rearrangements, using (25):

$$\frac{6D_e^{2/3}D_i^{1/3}\eta}{\gamma a_0} = \frac{\beta}{\sqrt[3]{|\alpha|}}\,. \tag{44}$$

From (24) and (23) it follows that in general $\beta \backsim \alpha \backsim 1$. Taking as plausible values $D_e \backsim 10^{-8}$ cm$^{2\cdot}$ sec^{-1} ; $D_i \backsim 10^{-7}$ cm$^{2\cdot}$ sec^{-1} ; $a_0 \backsim 10^{-3}$ cm., (44) requires that $\eta/\gamma \backsim 10^{-5}$ cm^{-1} sec., which is in agreement with a result found elsewhere from different considerations (Rashevsky, 1938c).

Requirement (43) together with (40) gives after rearrangements, using again (25):

$$a_0^3 > \frac{9\beta M D_i \gamma}{RT\mu q}\,, \tag{45}$$

which on account of (22) may be written (remembering $D_i >> D_e$)

$$a_0^3 > \beta a^{*3}\,. \tag{46}$$

Inequality (46) requires:

$$\frac{a_0^3}{a^{*3}} > \beta\,. \tag{47}$$

But, because of (33):

$$\frac{a_0^3}{a^{*3}} = \frac{V}{V_c} = \frac{2}{5}(\beta + 1)\,. \tag{48}$$

Hence (46) is equivalent to:

$$\frac{2}{5}(\beta + 1) > 2\beta\,,$$

or

$$\beta < \frac{2}{3}\,. \tag{49}$$

Inequality (48) gives now:

$$\frac{V}{V_c} < \frac{2}{3}\,, \tag{50}$$

and this, because of (24), makes

$$\alpha < 0\,. \tag{51}$$

Periodical contractions and expansions may thus exist under rather general conditions. Taking $V/V_c = 1/3$, which makes $\alpha = -1$, and which fixes q because of (23), since V is fixed by the choice of a_0, we find that $a_2 = 4{\cdot}65\, a_0$.

Putting

$$z = \frac{a}{a_0}\,; \quad D_i = nD_e\,, \tag{52}$$

the second fraction in the right-hand side of (9) may be written

$$\frac{1}{a_0}\,\frac{z^2 + 2n\sqrt{z}}{2z^3 + 4nz\sqrt{z} + 2n + 1}\,. \tag{53}$$

In our case we have $n = 10$; $z = 4{\cdot}65$. The first term in the denominator of (53) is equal to 200, the second to 400 and the last two to 21. The omission of the last two terms introduces an error of about 4%. Omitting $(2n + 1)$, (53) may be shortened by $z^2 + 2n\sqrt{z}$ and becomes equal to $1/2a_0z = 1/2a$.

This leads to equ. (10) as an approximation to (9), and we see that, with the values of the constants used here, the approximation is good.

With the values of the constants used above we find for the frequency

$$w = \sqrt{A_1B_2 - B_1A_2}$$

an expression inversely proportional to the square root of η. With $\eta\ .\ \backsim 10^6$ gm·cm$^{-1}\cdot$ sec^{-1}. which is a very high value, corresponding to a solid jelly, we have $w \backsim 10^{-3}$ sec^{-1}, giving a period of the order of hours. With smaller values of η the period can be made much smaller.

With slightly different values of the constants we may have:

$$A_1 + B_1 > 0\ ;\ (A_1 + B_1)^2 - (A_1B_2 - B_1A_2) < 0 \tag{54}$$

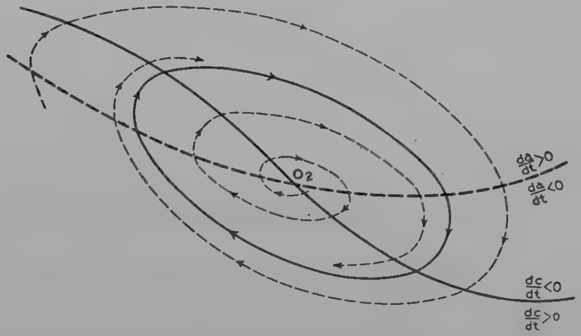

FIGURE 4

which will give oscillations with an *increasing amplitude.* The amplitude of course cannot increase indefinitely. What happens is shown on Fig. (4). In the neighborhood of O_2 the amplitude increases (broken line). Further away it decreases (broken line). Somewhere in between lies the stable closed path (full line), corresponding to undamped non-sinusoidal oscillations. An exact analytical treatment of the case presents a problem of great interest but of much greater difficulty than the present one.

It is of great interest to study possible cases in which the length of the cell oscillates periodically around an equilibrium value, so that the cell periodically contracts and expands. Such studies may eventually form a basis for the theory of amoeboid movements, or periodical contractions of tissues (heart).

II.

In Chapt. VI of MB we have shown on a limiting case that, in case of two interacting substances in a cell, periodical variations of their concentrations are possible. A. Weinberg (1938) has given a treatment of the problem for a more general case, using the exact solution of the diffusion equations for a sphere. Later on (Weinberg, 1939) he obtained the same results by using our new method, applicable to non-spherical shapes, developed in MB, Appendix.

If the concentrations and their gradients vary periodically, so will the diffusion forces vary also, and it is natural to expect that under the action of such periodic forces the deformation of the cell also varies periodically. A method somewhat similar to the one used above may be employed for treating that problem. We shall now have two substances, the average concentrations of which we shall denote by $\overline{c'}$ and $\overline{c''}$. The external concentration will be c_0' and c_0''. and all other constants referring to the two substances shall be marked by primes and double primes. We do not use subscripts $_1$ and $_2$ like in Chapt. VI of MB, because those subscripts have a different meaning in the derivation of equation (1) as given in a previous paper (Rashevsky, 1939). Using a method similar to Weinberg's (1939), we can now determine, for a prescribed a and b, the values c''^0 and c'^0, around which c' and c'' will oscillate. These values, plotted against a, will give us curves that are zero for $a = 0$ and for $a = \infty$. Due to the additivity of the diffusion forces, an equation, corresponding to equ. (5) will give us da/dt as a linear combination of c' and c''

$$\frac{da}{dt} = Ac' + Bc'' + C, \tag{55}$$

where A, B and C are functions of the reaction rates, diffusion coefficients, surface tension, etc. The requirement $da/dt = 0$ gives us then $Ac' + Bc''$ as a function of $a : Ac' + Bc'' = F(a)$. Since we also have c'^0 and c''^0 as functions of $a : c'^0 = F_1(a)$; $c''^0 = F_2(a)$; from the requirement $dc'/dt = 0$ and $dc''/dt = 0$, we can plot $Ac'^0 + Bc''^0 = AF_1(a) + BF_2(a)$ on the same diagram. The root of $F(a) = AF_1(a) + BF_2(a)$ gives then the values a_1 of a, for which $dc'/dt = dc''/dt = da/dt = 0$. The corresponding values $F_1(a_1)$ and $F_2(a_2)$ give us the values of c'_0 and c''_0, corresponding to that configuration. We may then investigate the behaviour of the system in the neighborhood of that configuration.

III.

The assumptions made in MB, Chapt. VI concerning the interaction of the two substances, which lead to equ. (20) and (21) are somewhat artificial. From the point of view of chemical kinetics it seems to be more plausible to assume, that the rate of production of the first substance is given by

$$\alpha_1(\beta_1 - \gamma_1\bar{c}'')\bar{c}' ,$$

indicating that the second substance inhibits the formation of the first. Similarly we may take for the rate of reaction of the second substance

$$-\alpha_2(\beta_2 - \gamma_2\bar{c}')\bar{c}'' ,$$

α_1, β_1, γ_1 etc. are constants, which are not to be confused with α, β and γ of section I.

Instead of equ. (3) we now have:

$$\frac{d\bar{c}'}{dt} = \alpha_1(\beta_1 - \gamma_1\bar{c}'')\bar{c}'$$
$$- \frac{3D_i'D_e'}{ab^2} \, \frac{b^2(D_e' + 2D_i') + 2(aD_e' + 2bD_i')}{(aD_e' + 2bD_i')(D_e' + 2D_i')} (\bar{c}' - c_0'), \tag{56}$$

$$\frac{d\bar{c}''}{dt} = -\alpha_2(\beta_2 - \gamma_2\bar{c}')\bar{c}''$$
$$- \frac{3D_i''D_e''}{ab^2} \, \frac{b^2(D_e'' + 2D_i'') + 2(aD_e'' + 2bD_i'')}{(aD_e'' + 2bD_i'')(D_e'' + 2D_i'')} (\bar{c}'' - c_0'') . \tag{57}$$

Consider the special case, when $c_0' = c_0'' = 0$ and when the cell is impermeable to the second substance, so that the latter does not flow either outward or inward. For instance $D_e'' = 0$; then

$$\frac{d\bar{c}'}{dt} = [\alpha_1\beta_1 - \frac{3D_i'D_e'}{ab^{\cdot 2}} \frac{b^{\cdot 2}(D_e' + 2D_i') + 2(aD_e' + 2bD_i')}{(aD_e' + 2bD_i')(D_e' + 2D_i')} - \gamma_1\bar{c}'']\bar{c}' \; ; \tag{58}$$

$$\frac{d\bar{c}''}{dt} = -\alpha_2(\beta_2 - \gamma_2\bar{c}')\,\bar{c}'' \; ; \tag{59}$$

which for a given constant a are of the form

$$\begin{aligned} \frac{d\bar{c}'}{dt} &= \bar{c}'(\lambda_1 - \mu_1\bar{c}'') \; ; \\ \frac{d\bar{c}''}{dt} &= -\bar{c}''(\lambda_2 - \mu_2\bar{c}') . \end{aligned} \tag{60}$$

Vito Volterra (1931) has shown that equ. (60) have *nondamped periodical* nonsinusoidal solutions under rather general conditions. It is therefore interesting to investigate whether the more general system (56) and (57) has similar solutions and then pass to the still more general case, by adding to the system (56) and (57) an equation corresponding to equ. (5).

The great biological interest of this type of equation lies in the fact that, whereas the linear cases have periodical undamped solutions only for rather restricted values of the constants, equation (60) have them *always* for positive values of λ_1, λ_2, μ_1 and μ_2. Moreover the solutions, while periodic, are not simple sinusoids and represent therefore a much more general type of oscillations. Volterra (1931, p. 56) has studied still more general systems, which have undamped oscillating, but *not periodical* solutions.

IV.

The considerations of this paper bear on two different but related biological problems. We have here a somewhat more general theory of nonspherical cells, than the one given previously (Rashevsky, 1938b). In the latter we required the vanishing of all principal stresses, a requirement which is not necessary for stable equilibrium. See also the correction to that paper, mentioned later (Rashevsky, 1939). Going back to section I, we remark that the equilibrium configuration O_2 is a function of q, D, T and γ. In the general case it will be also a function of h. A change of any of those parameters results in a change of a_2, hence in either a contraction or elongation of the cell. Such a contraction or elongation may therefore result either through a change of metabolic activities of the cell (change of q), or through a change of permeability (D and h), or through both. The same will hold for the more general cases, discussed in sections II and III. Moreover, things will be complicated by the possibility of periodic contractions and relaxations, which under circumstances may go on indefinitely. The importance of the above for a possible physico-mathematical theory of contractile tissues is evident. We do not wish to imply that the simple model discussed here is even remotely adequate to represent a real muscle-cell. But, in all our previous studies, we must begin with rather abstract oversimplified cases, which may not apply immediately to actual cases (MB, introduction). From this point of view the above considerations may be considered as laying down the foundations for a biophysical theory of contractility, which incidentally has the advantage of following naturally from our general mathematico-biophysical theory of the cell, in the course of a systematic development of the latter.

The actual force developed during the contraction of a cell studied here can be estimated by evaluating for instance σ_1. From equations (14) and (17) of MB, Appendix, we have, for $D_e = \infty$:

$$\sigma_{.} = \frac{2}{3} \frac{RT\mu q}{MD} \frac{a^2 b^2}{2a^2 + b^2} \tag{61}$$

with the values of the constants used in MB, and with $a \backsim b \backsim 10^{-3}$ cm, we have:

$$\sigma_1 \backsim 10^2 \, dyn{\cdot}cm^{-2} .$$

A threefold increase of a, and a tenfold decrease of D, which leaves the latter well within plausible limits (MB, p. 53). would give:

$$\sigma_1 \backsim 10^4 \, dyn{\cdot}cm^{-2} = 10 \, gr{\cdot}cm^{-2} .$$

A finite D_e does complicate the expressions, but does not change the order of magnitude.

Another biological phenomenon on which the foregoing considerations may have a bearing and the possible connection of which with contractility of tissues has been already pointed out (O. Furth, 1922) is that of amoeboidal movements. Our present discussion gives us a picture of a cell, which expands and contracts in one direction, not necessarily periodically. If noticeable inhomogeneities are present in the cell, these will produce strong asymmetries in the distribution of the forces, and may result in elongation in several directions and formation of protrusions like pseudopodia. The study of the above mentioned types of equations, which give oscillating but not periodical solutions (Volterra, p. 56) should be of particular interest in this connection. It is also to be remarked, that any nonuniformities of the cell, due to *coarse* inclusions, will be subject to statistical fluctuations, which will impart a degree of irregularity to the movement of the cell, If we have N coarse particles per element of volume, the average fluctuation from the mean is equal to $1/\sqrt{N}$ (Gyemant, 1925). With 1000 coarse particles distributed at random in a cell, the average fluctuation in a volume equal to 1/10 of the cell volume, and containing therefore on the average 100 particles, will be 10%. This will affect the distribution of the gradients and forces by about as much and will result in rather irregular movements. This leads to an interesting problem of the combined effects of regular periodicities and of statistical fluctuations.

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CONCERNING RASHEVSKY'S THEORY OF THE "GESTALT"

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In experiments of Klüver on monkeys and of Hertz on bees, observed reactions indicate the presence of a neural mechanism which serves to order geometric figures in a linear sequence, so that any given figure occupies a definite place in a one-dimensional array. In a theoretical mechanism described by Rashevsky, presentation of a visual stimulus-figure results in an excitation at a given center whose intensity is a function of the contour of the figure. This functional dependence of excitation upon the curve is examined in some special cases, and the mode of variation is further described qualitatively.

I. The Problem

In the course of an extensive series of experiments performed by Klüver (**1**), a monkey is presented with two boxes, identical except that the nearest face of one has on it a large rectangle, while that of the other has a (nearly) similar rectangle of half the area. By putting food in the first box and none in the second during a period of training, the monkey is trained to react "positively" to the larger rectangle. After a period of such training the pair of rectangles on the boxes is replaced by another pair having the same relative but different absolute sizes. It is found that, unless the absolute sizes are made very small or very large, the monkey continues to react positively to the larger rectangle, even though this may be identical with the smaller of the pair used in training. Moreover, if the pair of rectangles is replaced by a pair of figures having any one of a variety of different shapes, similar to one another and with areas in the ratio approximately 2 to 1, then the monkey still chooses the larger figure.

This type of experiment is varied in a number of different ways and the results do not seem intuitively surprising. However, a somewhat more mystifying outcome is obtained when pairs of different shapes of approximately the same area are utilized, e.g., a circle and a square. After the training with this pair of stimuli, the circle and the square are replaced by some other pair of distinct shapes. In general one of these shapes was chosen to give a certain impression of roundedness, the other of angularity. Then through quite a wide range of such stimulus-pairs the number of positive reactions to one was clearly in excess of the number of positive reactions to the other.

On the other hand, with certain other pairs the reactions were equally divided.

In the first experiment mentioned there is present with each stimulus-pair an obvious ordering relation, the same for all, with respect to which the two stimuli in each pair can be ordered. This relation is evidently that of being-greater-than, and *a priori* it might equally well refer to areas or to perimeters. We may therefore think of the monkey's training as conditioning him to react to the first member of the ordered pair. A theoretical mechanism capable of this type of conditioning has already been described (**3**, ch. XXVI).

The results of the other experiment can be made intelligible, when viewed in the light of the first, provided we can exhibit a common ordering relation of such a nature that the order is clear in the pairs between which the monkey's choice was unequivocal, but obscure where the choice was random. Concretely, we require an arrangement of neurones, terminating in a single neurone or set of neurones, and transmitting to each terminal neurone an excitation whose intensity is a function only of the shape of the visual image. Then if the initial training conditions the animal to react positively to the shape yielding the excitation, say, of greatest intensity, we should expect for any other pair of shapes a clear preference again for the shape of greatest intensity, if these intensities are significantly different, but a random choice when they are (nearly) the same.

Experiments performed by Hertz (**4**) on bees exhibit a fairly well-defined order of natural preference among the numerous shapes presented, quite apart from experimental conditioning. In general the bees prefer an abundance of detail within the total area covered, and they prefer small figures to large. However, Hertz distinguishes between "figural intensity," dependent upon the total perimeter, and "figural quality," and finds a preference often clearly exhibited for a shape of one figural quality over another of different quality but equal intensity. Thus the intensity of excitation, on our theory, is a function both of Hertz's figural intensity and of figural quality.

Rashevsky has demonstrated the possibility of such an association between shapes and intensity of excitation by his fruitful picture of a succession of intra-inhibiting synaptic levels (**3**, esp. ch. XXVII, XXVIII). The excitation is relayed from the initial sensory to the ultimate motor level, the transmission from any level to the next being effected by a group of neurones whose arrangement determines the particular features of the distribution that are to be kept invariant.

Now consider any one of the stimulus shapes S. Suppose the illumination, color, etc., to be uniform and the same for all, and assume, in fact, that only the contour C_0 is illuminated. With a suitable arrangement of preceding neurones, the excited synapses at some level will be arranged in a curve which is geometrically similar to the presented contour C_0. This is, therefore, a closed curve C. Suppose the synapses comprising this level are uniformly distributed and numerous enough to be regarded, with sufficient approximation, as mathematically dense.

Now suppose that each excited synapse inhibits each other synapse proportionally to its own excitation and to a function of its distance from this other synapse; then if s and t are the arc lengths measured along C from some fixed point of C to two given points, if $r(s, t) = r(t, s)$ is the ordinary distance between these points, and if $\phi(t)$ is the resultant excitation per unit arc length at t, then the inhibiting effect of t upon s can be written $\lambda K(r)\phi(t)$, where λ is some constant and K some positive function of r. Then the total inhibition acting on s is

$$\lambda \int K(r)\phi(t)\,dt\,,$$

where the integration is made around the entire curve C. Thus the resultant steady state excitation (per unit length) *per unit of impressed excitation* is given by the solution $\phi(s)$ of the integral equation (**3**, ch. XXVII)

$$\phi(s) = 1 - \lambda \int K(r)\phi(t)\,dt\,. \qquad (1)$$

If all synapses at this level are connected to a single synapse at the next level, then the total excitation at this synapse will be measured by

$$\Phi = \int \phi(s)\,ds\,. \qquad (2)$$

For a fixed inhibitory function K, Φ is a functional, dependent upon the particular contour C about which excitation takes place. The relation between the values of Φ for contours of different shapes furnishes the ordering relation sought.

II. Some Numerical Approximations

We wish to investigate the dependence of the total excitation Φ upon the shape of the curve C, when the inhibition function K is a given function of r. Evidently the curves C should be taken with constant length. Actually, in any experimental check, the area, too, should be kept fixed. In the present preliminary investigation, however, we keep only the perimeter constant. It is no restriction to take this perimeter as the unit of length, so that the limits 0 and 1 should be put on the integrals in (1) and (2).

We note that the simplest curve of all is the circle, for which the excitation is always constant whatever function $K(r)$ is used. The solution of the integral equation can then always be obtained in closed form. Let

$$k = \int_0^1 K(r)\,dt\,. \tag{3}$$

Then k is independent of s for the circle, and the solution to (1) is

$$\phi = (1 + \lambda\, k)^{-1}\,. \tag{4}$$

Since the circumference is of unit length this is also the value of Φ. For a fixed k, Φ vanishes asymptotically as λ increases, and for all positive λ, Φ is less than unity.

A priori it seems plausible that the inhibiting effect should be greatest between nearest centers, and that K, therefore, should be a decreasing function of r. A single increasing function was tried in two cases, viz., $K = r^2$, for the circle, and for a double line-segment regarded as a rectangle of zero area. For these two cases, with $\lambda = 1$, Φ turned out to be .9518 and .9603, respectively, and this small difference for such different shapes was regarded as further evidence that an increasing function was uninteresting for this investigation.

A natural choice for a positive decreasing function is r^{-1}. However, checking with the circle shows that for a power of r whose exponent is —*1* or less, the solution does not exist. Evidently the inhibiting effect could not become actually infinite. But assuming the effect to vary approximately as r^{-1}, though never exceeding some finite value, the function finally chosen was

$$K = (a + r)^{-1}\,, \qquad a = 10^{-2}\,. \tag{5}$$

The constant a was taken as of the order of magnitude of the distance between adjacent synapses.

As a closed solution cannot be hoped for in general, a method of approximate solution was employed similar to a method described by Nyström (**2**). The Neumann series solution of the integral equation giving the solution as a power series in λ is obtained by first replacing the ϕ in the integrand by $\phi_1 = 1$ (the impressed excitation in our case, which is constant) to get ϕ_2, then replacing ϕ by ϕ_2 to get ϕ_3, and so on. But these quadratures themselves become excessively complicated if not impossible, and so are approximated by a suitable method of numerical quadrature. Thus if one tabulates the values of K for a sufficient number of $(s\,, t)$-values, and for each s calculates the quantities $K(s\,, t)\,\phi_i(t)$, then the numerical quadrature gives the approximate value of $\phi_{i+1}(s)$.

If, for each s and r, $K(s, t)\phi(t)$ were continuous and had a continuous derivative in t, then the most suitable method of numerical quadrature would be Gauss's or Tchebyscheff's. Actually, however, for $0 < s < 1$ this function of t rises to a single maximum, on each side of which the curve is concave upward, and at which the derivative is discontinuous. Therefore Simpson's rule seemed to be the only feasible method. But again Simpson's rule approximates to the curve in question by a set of parabolic arcs, each arc being determined by three consecutive points of subdivision. Evidently if the peak point were the middle point of a triple determining such an arc, this arc would give a very poor approximation. Hence, whenever the peak point entered as an even point of subdivision (counting the end-point as the first) the first and last arcs were approximated by line-segments, and Simpson's rule was employed on the intermediate portion.

Further consideration made it possible to lighten the labor somewhat. Evidently $\phi_1 = 1$ is not the only possible choice of function with which to start. In fact, suppose that $\bar{\phi}_1$ and $\bar{\bar{\phi}}_1$ are two functions satisfying

$$1 \geqslant \bar{\bar{\phi}}_1 \geqslant \bar{\phi}_1 \geqslant \phi$$

for all s. Then, since $K > 0$, we have

$$0 \leq \bar{\bar{\phi}}_2 \leq \bar{\phi}_2 \leq \phi,$$

where $\bar{\phi}_2$ and $\bar{\bar{\phi}}_2$ are obtained by substituting $\bar{\phi}_1$ and $\bar{\bar{\phi}}_1$ respectively in place of ϕ in the right member of (1). Moreover, if

$$1 \geqslant \bar{\phi}_1 \geqslant \phi \geqslant \bar{\bar{\phi}}_1 \geqslant 0,$$

$$\bar{\phi}_1 \geqslant \phi_1 \geqslant \bar{\bar{\phi}}_1,$$

where ϕ_1, $\bar{\phi}_1$ and $\bar{\bar{\phi}}_1$ are otherwise arbitrary, then

$$\bar{\phi}_2 \leq \phi_2 \leq \bar{\bar{\phi}}_2.$$

Now $\phi_1 = 1$ is everywhere too large, and the resulting ϕ_2 therefore too small. But if any approximation were known in advance to be better than $\phi_1 = 1$, then the corresponding sequence of approximations would stabilize more rapidly. In practice it appeared advantageous to start with a suitable ϕ_1, obtain ϕ_2 by quadrature, and take for ϕ_3 some weighted mean.

Consider now some actual results, starting with the circle for which the solution is exact. We find from (3) and (5) that

$$k = 4.1835\,,$$

so that (4) gives

$$\phi = \Phi = (1 + 4.1835\,\lambda)^{-1}\,. \tag{6}$$

For a few values of λ we have

$$\begin{array}{llll} \lambda = 1\,, & 0.05\,, & 0.02\,, & 0.005 \\ \Phi = 0.193\,, & 0.827\,, & 0.923\,, & 0.980 \end{array} \tag{7}$$

Note that the successive steps of the numerical method outlined above, if applied here with $\phi_1 = 1$, correspond to the sums for increasing n of the first n terms of the expansion of (6) in powers of λ. However, this does not converge except for $\lambda = .2$ or less. The significance of this becomes clear when we consider for a moment the physical picture. When excitation first occurs it is momentarily uniform and free of mutual inhibition. As nearby centers have time to act, if the inhibiting effect is too great there will result a complete annihilation of excitation. But this would also destroy the inhibition and allow a re-establishment of excitation. Such an oscillation might go on indefinitely without a steady state being possible.

To follow the dynamics in complete detail, would require some assumptions, or information, about the time-rate of inhibiting action. Hence we shall assumeλ to be small enough to permit the rapid establishment of a steady state. In fact, we shall assume it small enough so that the *initial* inhibitory action *nowhere completely* inhibits. Hence every approximation $\bar{\phi} > 0$ everywhere on the curve.

The next curve considered was the double line-segment, regarded as the limit of a rectangle of dimensions $(\frac{1}{2} - \varepsilon) \times \varepsilon$. From symmetry,

$$\phi(s) = \phi(1/2 \pm s) = \phi(1 - s)\,. \tag{8}$$

Hence we need consider only the interval $0 \leq s \leq \frac{1}{4}$, and the equation can be transformed to

$$\phi(s) = 1 - 2\,\lambda \int_0^{1/4} \{.51 - s - t)^{-1} + (.01 - |s - t|)^{-1}\}\phi(t)\,dt\,. \tag{9}$$

The first quadrature required in the Neumann series can be carried out exactly to give the first approximation

$$\phi_1(s) = 1 - 2\,\lambda \log(1 + 100s)\,(51 - 100s)\,. \tag{10}$$

Ten subintervals were used.

For $\lambda = .005$, we find

t	ϕ_1	ϕ_2
.000	.9607	.9614
.025	.9487	.9448
.050	.9438	.9445
.075	.9409	.9376
.100	.9389	.9401
.125	.9375	.9347
.150	.9365	.9379
.175	.9357	.9330
.200	.9352	.9369
.225	.9349	.9338
.250	.9348	.9365

$$\int_0^1 \phi_1 dt = .9399 , \qquad \int_0^1 \phi_2 dt = .9384 . \tag{11}$$

As we have seen, ϕ_1 must be too small and ϕ_2, if computed exactly, would be too large. Hence our values for ϕ_2 cannot be accepted. The true value of Φ is somewhat in excess of .940, and better results could be obtained only by increasing the number of subdivisions.

For $\lambda = .02$, several successive substitutions and means were taken. The last two sets obtained are:

t	ϕ_n	ϕ_{n+1}
.000	.8675	.8673
.025	.8193	.8177
.050	.8106	.8105
.075	.8018	.8009
.100	.7963	.7966
.125	.7922	.7925
.150	.7894	.7900
.175	.7872	.7877
.200	.7860	.7869
.225	.7789	.7786
.250	.7850	.7861

$$\int_0^1 \phi_n \, dt = .7978 , \qquad \int_0^1 \phi_{n+1} \, dt = .7977 . \tag{12}$$

For $\lambda = .05$, we found

t	ϕ_6	ϕ_7
.000	.731	.7418
.025	.637	.6491
.050	.622	.6386
.075	.608	.6240
.100	.599	.6162
.125	.593	.6099
.150	.588	.6062
.175	.585	.6030
.200	.583	.6015
.225	.581	.6002
.250	.581	.6001

$$\int_0^1 \phi_6 \, dt = .604 , \qquad \int_0^1 \phi_7 \, dt = .6204 . \tag{13}$$

Here ϕ_6 was an arithmetic mean, and ϕ_7 obtained from the quadrature.

For $\lambda = .1$, ϕ_1 is negative except near the ends of the segment. The calculations were therefore not continued.

As with the circle, Φ decreases rapidly as λ increases. For a fixed λ, ϕ increases rapidly on approaching the ends of the segment. On approaching the midpoint of the segment ϕ decreases, but very slowly. This is pretty much what would be expected intuitively.

The next curve to be considered was the Greek cross with limbs of negligible width. Since for this

$$\begin{aligned}\phi(s) &= \phi(1/4 \pm s) = \phi(1/2 \pm s) \\ &= \phi(3/4 \pm s) = \phi(1 - s),\end{aligned} \tag{14}$$

we consider only the interval $0 \leq s \leq 1/8$, and reduce the integral equation to

$$\begin{aligned}\phi(s) = 1 - 2\lambda \int_0^{1/8} \{ [.01 + |t - s|]^{-1} + [.26 - t - s]^{-1} \\ + 2 [.01 + \{ (\tfrac{1}{8} - s)^2 + (\tfrac{1}{8} - t)^2 \}^{\frac{1}{2}}]^{-1} \} \phi(t) \, dt .\end{aligned} \tag{15}$$

For $\lambda = .05$ the first quadrature gives negative values of ϕ_2. We consider only $\lambda = .02$.

The method employed here was altered slightly by starting with only a single subdivision and then adding more as a fair degree of stability was obtained. The single subdivision gave ultimately:

t	ϕ_6	ϕ_7
0	.8308	.8295
1/16	.7015	.6983
1/8	.6418	.6365

Interpolation gave approximate values of ϕ_7 for $t = 1/32$ and $t = 3/32$, and the process was carried on with four intervals of subdivision. Ultimately we found:

t	ϕ_{10}	ϕ_{11}
0	.8465	.8417
1/32	.7785	.7765
1/16	.7626	.7602
3/32	.7252	.7222
1/8	.6782	.6742

A final subdivision gave:

t	ϕ_{13}	ϕ_{14}
0	.8457	.8465
1/64	.8083	.8095
1/32	.7894	.7953
3/64	.7770	.7838
1/16	.7671	.7685
5/64	.7518	.7547
3/32	.7345	.7389
7/64	.7113	.7151
1/8	.6859	.6895

$$\int_0^1 \phi_{13}\, dt = .7628\,, \qquad \int_0^1 \phi_{14}\, dt = .7664\,. \tag{16}$$

Noting that increasing the number of subdivisions increases the values of ϕ at stabilization, we may regard ϕ_{14} as fairly accurate.

These results, rough and incomplete as they are, furnish nevertheless some indications as to the type of effects one may expect from such mutual inhibitions. Comparing the three contours, circle, rectangle of zero area, and Greek cross of zero area, for the case $\lambda = .02$, we see that the constant excitation around the circle is greater than the maximum excitation for either of the other two. At the end of the rectangle and at the end of the arm of the cross, the excitations are not greatly different, whereas at the middle the excitations differ by about one-tenth. The total excitations for these two contours are about .80 and .77 respectively, as compared with the value .92 for the circle. One must observe at this point that these total excitations are applied to neurones whose thresholds may be not greatly different. Hence effective differences between these excitations are not within a range of 12 per cent or 15 per cent as they appear at first glance, but may well run up to several hundred per cent when, say, the neurone has a threshold of .75.

In general we may expect "corner" and "overlap" effects of diminished excitation near corners and points of high curvature, and also on arcs which lie close together. Hence decreasing the area, and so bringing the arcs closer together, should tend, in general, to cut down the total excitation. And again, cutting down the maximum distance between pairs of points, even though the area remains the same, amounting to increasing the curvature and the number of corners, would diminish the excitation. Thus "jagged" curves, with numerous corners and crinkles, will yield low excitation, while rounded, full curves, ellipses with small eccentricities, will have a higher excitation.

III. Some General Considerations

An analysis in general along some such lines as the following seems indicated. Let $K(r)$ be a properly monotonically decreasing function of r possessing suitable continuity properties. Consider the integral equation (1) associated with any closed curve C of unit length, which is continuous and whose derivatives have at most a finite number of points of discontinuity. If C does not intersect itself, then it bounds a region of the plane of a certain area. We may thus inquire,

(a) What curve C enclosing a given area gives to Φ as defined by (2) the largest possible value? One would expect to find a unique curve C_A, bounding a region of given area, A, for which $\Phi = \Phi_A$ is a maximum. If so, we may inquire

(b) Is Φ_A an increasing function of A? It seems likely that C_A would turn out to be everywhere convex, possibly an ellipse, and that Φ_A is increasing. If so, the circle would furnish an absolute maximum for all A, since it bounds the greatest possible area. For a given curve C which encloses an area A and is different from C_A, one may then hope to find all curves enclosing the same area and having the same total excitation Φ as C.

Similarly one could ask for a curve with given area giving Φ a minimum value.

In making such an investigation it would be necessary to require that

$$\lambda K \leq 1$$

in order to insure that a steady state can be reached for any curve whatsoever. With this condition the sum of the first two terms of the Neumann series will be positive at every point of any curve.

It is hopeless at present to attempt any detailed check of this theory against experimental results. It has been the aim of this presentation only to show that some linear ordering is possible, and to indicate for a particular method of ordering [a particular $K(r)$] how the figures would be ordered. However, we may note that in the experiments of both Klüver and of Hertz, the contrasting features are smoothness as against angularity, simplicity as against detail, and this contrast precisely is obtained by the sharply decreasing functions $K(r)$ here used as a measure of the inhibitions. Furthermore, it is just such a function which seems indicated from simple physiological considerations — nearby centers should affect one another more strongly than distant ones. Replacing the kernel $(a + r)^{-1}$ by another function $K(r)$ should alter only details, not the general character of the ordering. Hertz' results, then, seem to indicate a preference for figures giving lower excitations.

Evidently there is involved not only the pure form, but also the size. The important element in the size may be the total perimeter; it may be the area enclosed by the contour; it may be the area of the smallest convex region enclosing the contour; it may be a combination of all of these. Quite likely the ratio of these two areas, as a measure of the complexity, would be important. At any rate, any experimental checking of such a mechanism requires keeping constant as many of these elements as possible while varying the form.

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